Biopharmaceutical Sector

Weekly Update – March 11, 2024

STIFEL | Healthcare

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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:

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Feb 19, 2024 (Big Drugs, Autoantibodies)
Feb 12, 2024 (Fibrosis, Endometriosis)
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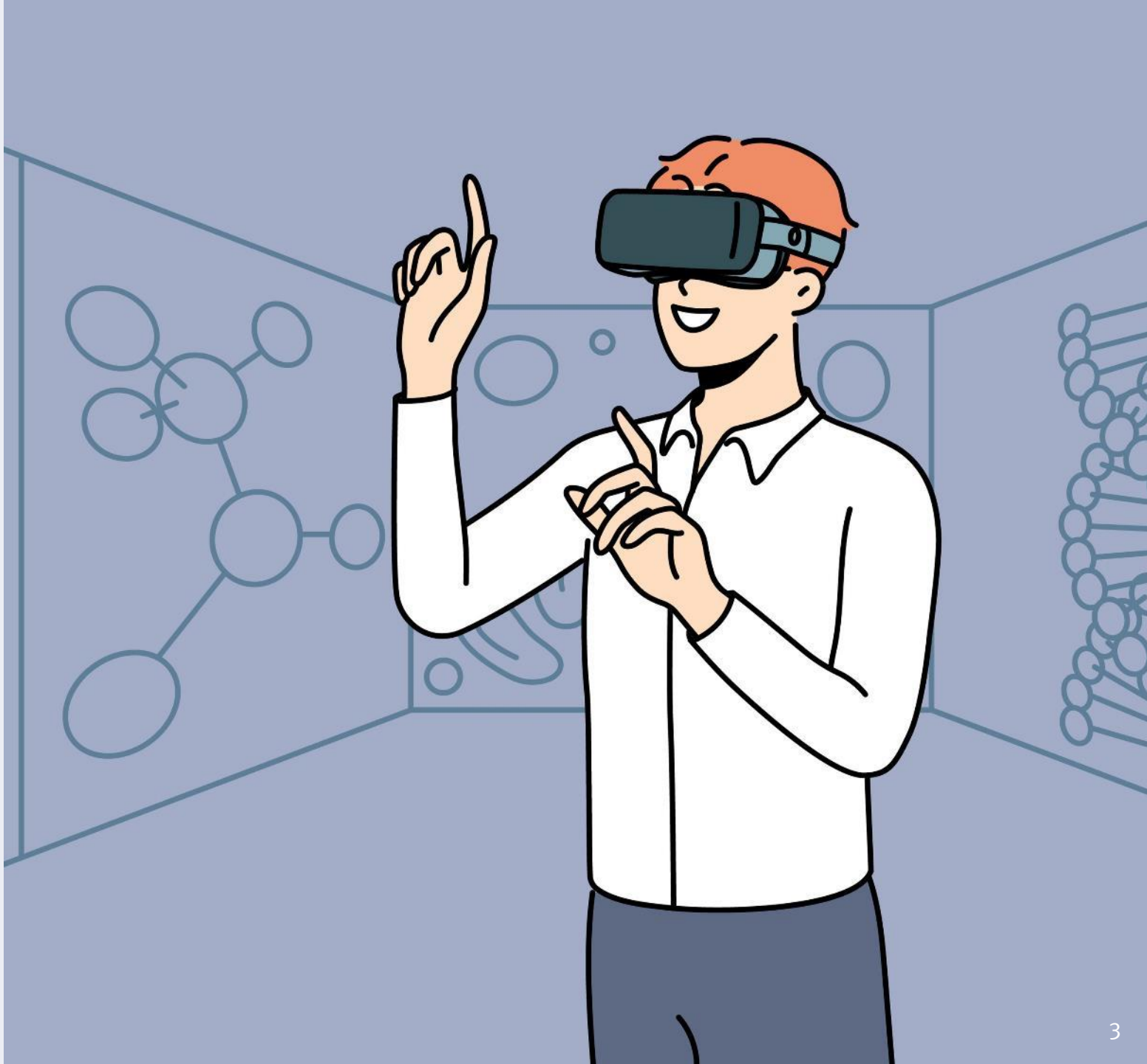

Stifel Active in Biophama Sector Advisory and Financing Transactions

Today, biopharma companies find themselves in a fast-moving environment characterized by great opportunity. This environment calls for getting the best possible advisor by your side. Stifel's Global Healthcare Group brings senior level attention and intense focus on execution to its clients. The group has been active in 2024's dynamic financing and deal environment. Since the formation of the Global Healthcare Group in 2010, Stifel's team has helped to raise over $115 billion in over 600 transactions and has advised on over 150 strategic transactions.

$420,000,000

Apogee Therapeutics

Follow-On Offering

Joint Bookrunner

March 2024

$140,000,000

REGENXBIO

Follow-On Offering

Joint Bookrunner

March 2024

$632,500,000

Viking Therapeutics

Follow-On Offering

Joint Bookrunner

February 2024

$160,125,000

KalVista Pharmaceuticals

Follow-On Offering

Joint Bookrunner

February 2024

UPSHER-SMITH

Has agreed to be acquired by

Bora Pharmaceuticals

Advisor to Seller

Pending

€50,500,000

Sensorion

PIPE

Lead Placement Agent

February 2024

$147,900,000

ALTO NEUROSCIENCE

Initial Public Offering

Joint Bookrunner

February 2024

$230,000,000

Dianthus Therapeutics

PIPE

Joint Placement Agent

January 2024

$345,144,000

Dyne Therapeutics

Follow-On Offering

Joint Bookrunner

January 2024

$175,000,000

PROPELLA

Has been acquired by

astellas

Advisor to Seller

December 2023

$230,000,000

Syndax

Confidentially Marketed Follow-on Offering

Joint Bookrunner

December 2023

$180,000,000

SPYRE THERAPEUTICS

PIPE

Co-Lead Placement Agent

December 2023

$100,000,000

VANDA PHARMACEUTICALS INC.

Has acquired U.S. and Canada rights to

Ponvory (ponesimod)

from

Johnson&Johnson

Advisor to Buyer

December 2023

$245,000,000+

TEIJIN

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

ascendis pharma

Advisor to Licensee

November 2023

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Join Us at Biotech Hangout This Friday

Biotech Hangout held its latest event on March 8, 2024.

The next event will be on March 15, 2024.

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

Macro Update

Powell: Fed Is ‘Not Far’ From Gaining Confidence Needed to Cut Rates

Nick Timiraos, *Wall Street Journal*, March 7, 2024 (excerpt)

Federal Reserve Chair Jerome Powell told lawmakers the central bank was “not far” from being able to cut interest rates and that rates were far above levels that might be anticipated during periods of mild inflation and moderate growth.

Powell repeated his view Thursday that the central bank was looking for greater confidence that inflation was returning to its 2% target, but he went one step further during his second day of testimony on Capitol Hill by qualifying how soon the Fed might get there.

“When we do get that confidence, and we’re not far from it, it will be appropriate to dial back” interest rates to avoid tipping the economy into a recession, he said.

Powell had signaled earlier that the Fed wasn’t considering a rate cut at its next meeting, March 19-20, which has shifted attention to whether the central bank might be in a position to cut rates around the middle of the year.

Powell also said he thought interest rates “now are well into restrictive territory.” Central banks sometimes judge their interest-rate stance against estimates of a so-called neutral rate that might be expected during times when supply and demand are at equilibrium in the economy.

Rates are “well above neutral,” he said. “We’re far from neutral now.”

Source: https://www.wsj.com/economy/central-banking/powell-fed-is-not-far-from-gaining-confidence-needed-to-cut-rates-75c9b061

Central Bankers See Victory Within Reach in Push To Tame Inflation

Martin Arnold, Claire Jones and Mary McDougall, *Financial Times*, March 8, 2024 (excerpt)

Top central bankers in Europe and the US have moved closer to declaring victory over the biggest inflation surge for a generation, with new data giving policymakers confidence they can cut rates by the summer.

On Friday, US jobs growth figures for December and January were downgraded sharply, cementing investors' expectations of a rate cut by June, while eurozone data showed wage and profit growth easing.

Federal Reserve chair Jay Powell said on Thursday that the US central bank was "not far" from having the confidence to start lowering borrowing costs.

European Central Bank president Christine Lagarde said policymakers had "begun discussing the dialling back of our restrictive stance", celebrating "good progress towards our inflation target", even if "we are not there yet".

"I found them very dovish in sync," Ludovic Subran, chief economist at insurer Allianz, said of Powell and Lagarde. "The question now is whether the Fed will wait to cut rates until September."

Friday's US data showed that the economy added 275,000 jobs last month, beating forecasts, but big downgrades to previous figures bolstered expectations that the first cut could come by June.

In the eurozone, fourth-quarter data showed unit labour costs and profit margins rising by a slower rate, easing fears that companies are driving up inflation by passing on higher labour costs via aggressive price rises.

Source: https://www.ft.com/content/76d07a7e-3af4-4024-854f-61828ad1b25a

Biopharma Market Update

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

The XBI Closed at 98.95 Last Friday (Mar 8), Down 2.5% for the Week

The XBI is up 10.8% since the year began. The biotech market was soft last week as negative stock specific news hit the sector from a number of quarters.

Biotech Stocks Down a Little Last Week

Return: Mar 2 to Mar 8, 2024

Nasdaq Biotech Index: -1.2%
Arca XBI ETF: -2.5%
Stifel Global Biotech EV (adjusted): +1.5%*
S&P 500: -0.3%

Return: Jan 1 to Mar 8, 2024

Nasdaq Biotech Index: +2.0%
Arca XBI ETF: +10.8%
Stifel Global Biotech EV (adjusted): +21.5%*
S&P 500: +7.4%

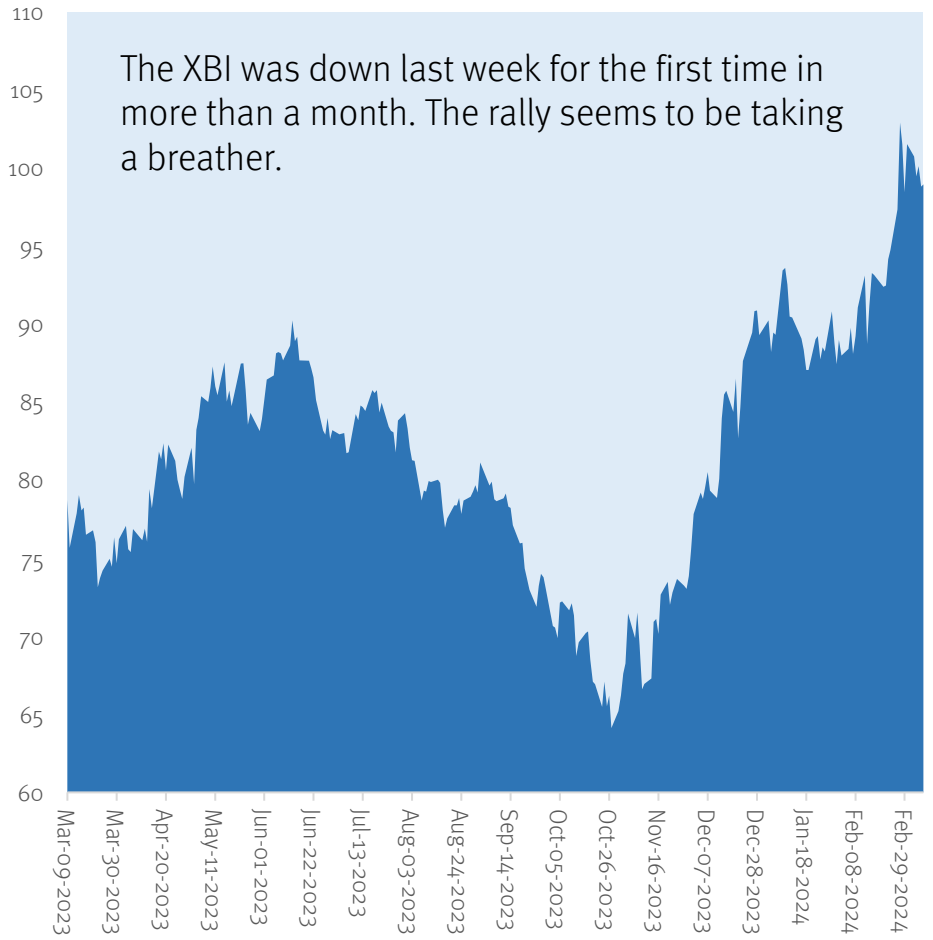
VIX Up

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 1, 2024: 13.1%
Mar 8, 2024: 14.7%

10-Year Treasury Yield Down

Jan 20, 2023: 3.48%
May 26, 2023: 3.8%
July 21, 2023: 3.84%
Sep 29, 2023: 4.59%
Dec 29, 2023: 3.88%
Jan 26, 2024: 4.15%
Feb 23, 2024: 4.26%
Mar 1, 2024: 4.19%
Mar 8, 2024: 4.13%

XBI, March 9, 2023 to March 9, 2024



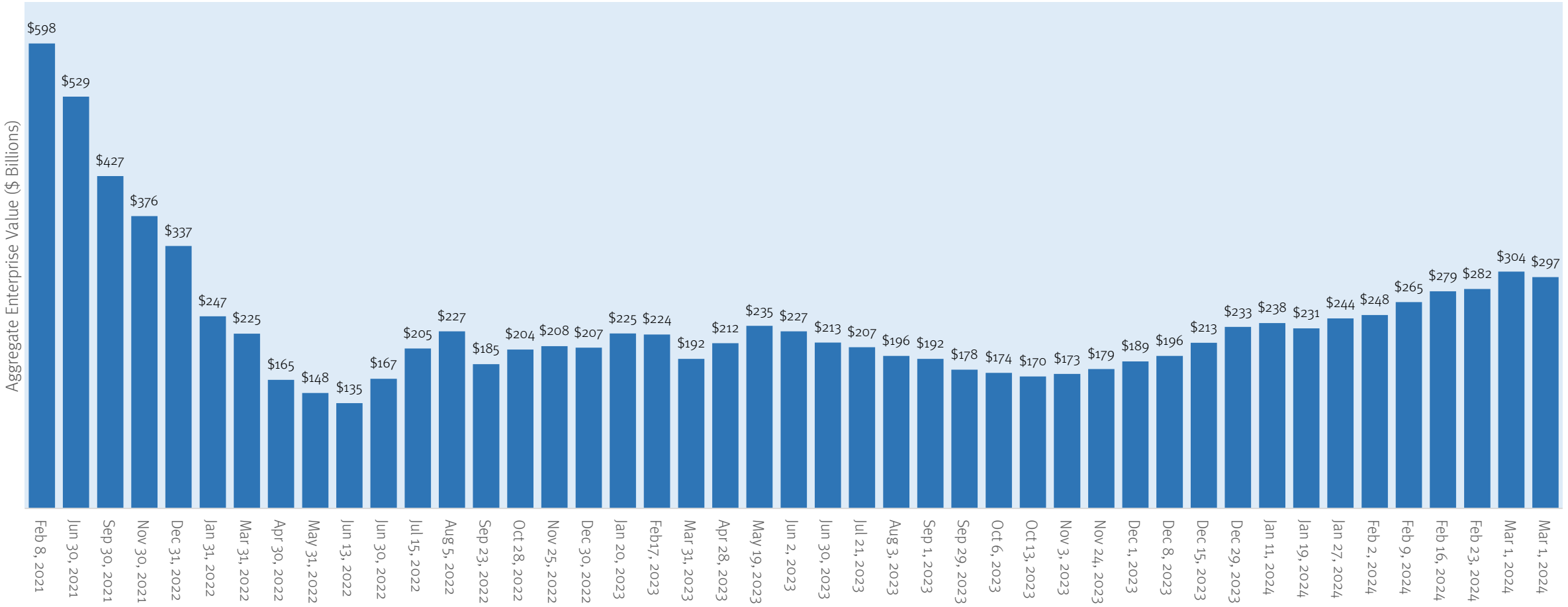
Source: S&P Capital IQ and Stifel analysis

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

Total Global Biotech Sector Value Dropped 1.7% Last Week

The total enterprise value of the global biotech sector is up 30% for the year to date on an addition/exit corrected basis. The rally that started last November stopped briefly last week. The biggest decliner last week was Viking (down 21.4%). Its drop accounted for over a third of the market drop.

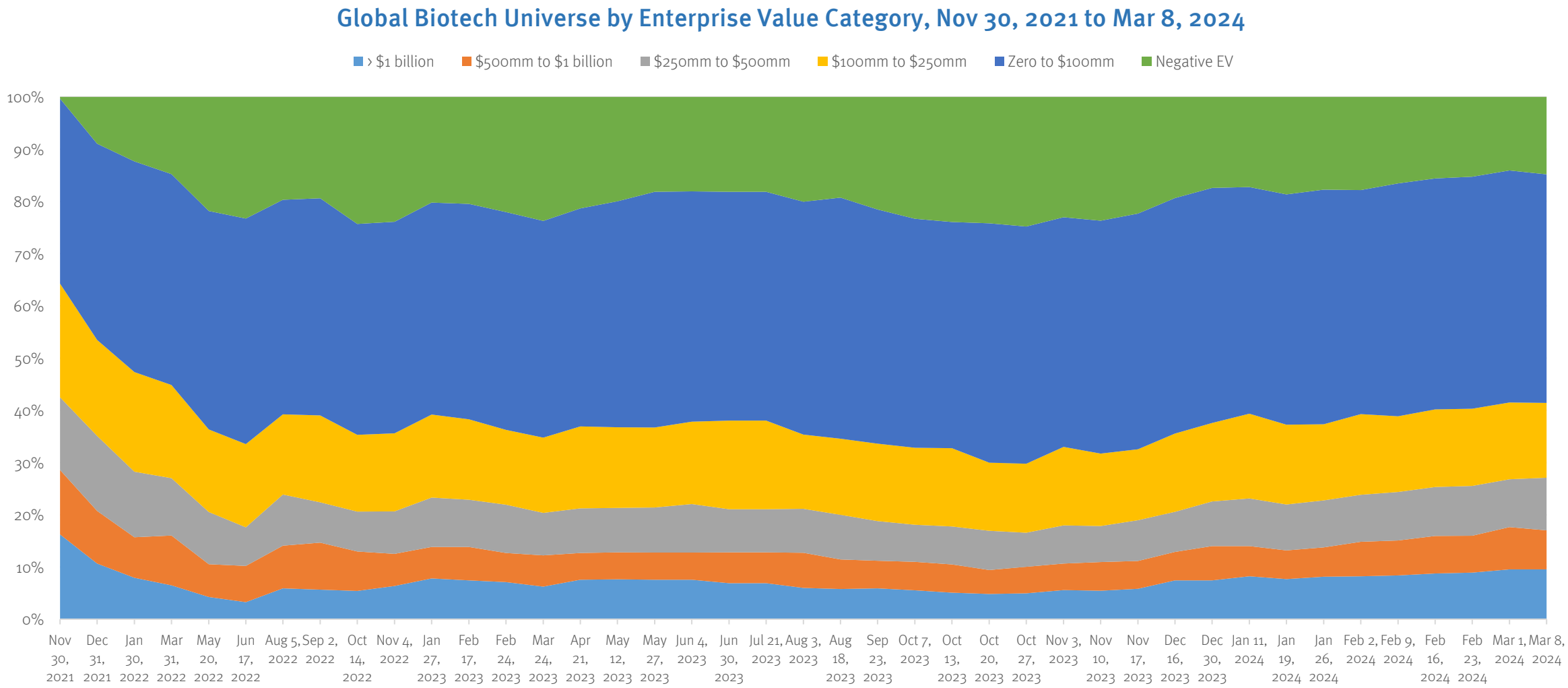
Total Enterprise Value of Publicly Traded Global Biotech, Feb 8, 2021 to Mar 8, 2024 ($ Billions)



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

Global Biotech Neighborhood Analysis

Last week saw no change in the number of biotechs worth less than $100mm.



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

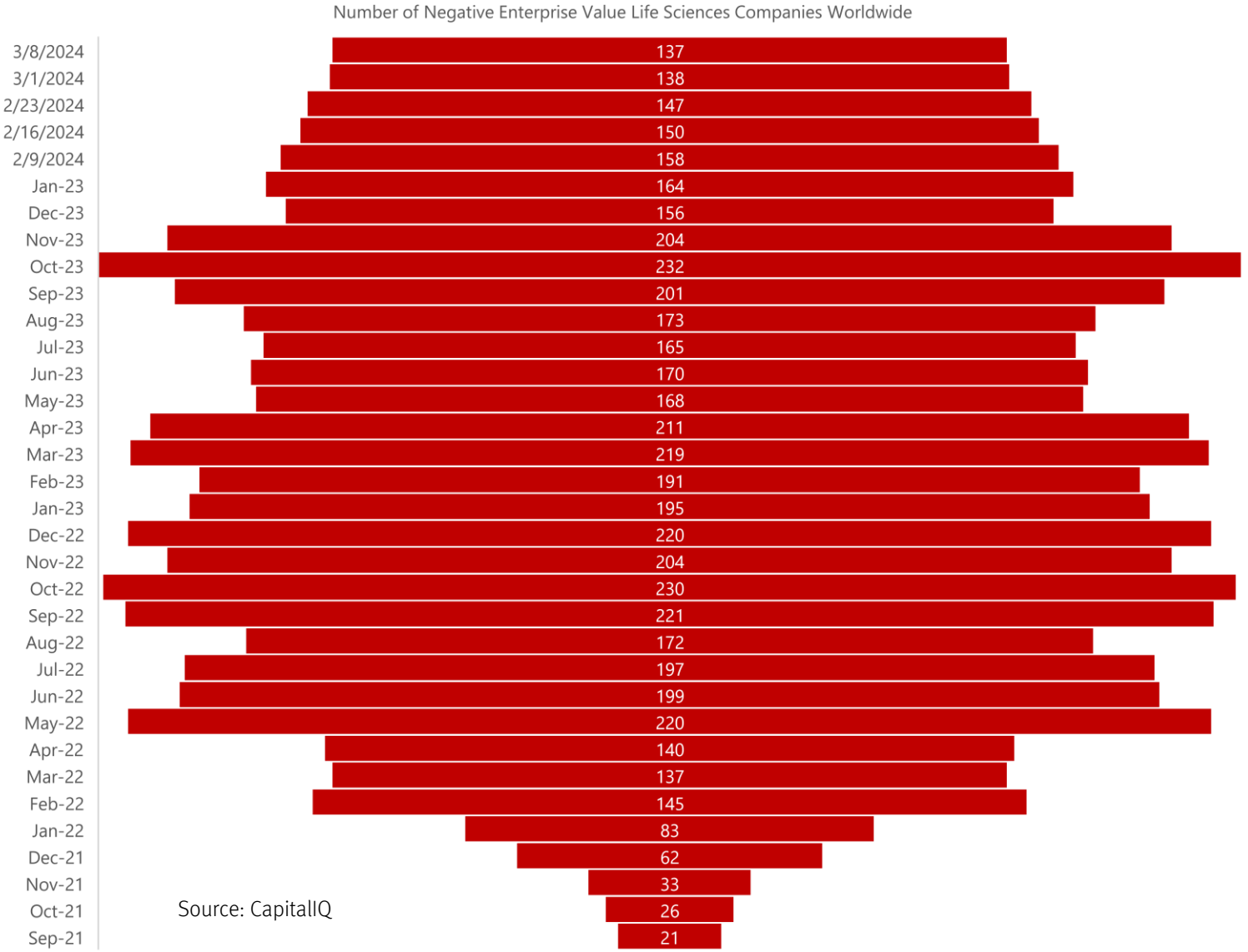
Life Sciences Sector Total Value Up Last Week by 0.2%

Last week saw the life sciences sector gain $68 billion in value. The best performing sectors were CDMO's and diagnostics.

Sector	Firm Count	Enterprise Value (Mar 8, 2024, $millions)	Change in Last Week (percent)	Change in Last Month (percent)	Change in Last Year (percent)
API	81	$80,895	-0.5%	1.8%	0.0%
Biotech	803	$297,135	-1.7%	14.4%	-5.1%
CDMO	40	$152,336	2.8%	3.8%	-17.2%
Diagnostics	81	$282,644	2.2%	3.6%	8.9%
OTC	30	$27,931	2.0%	0.5%	-4.0%
Commercial Pharma	719	$6,298,774	0.4%	3.8%	16.4%
Pharma Services	39	$199,637	-0.2%	6.0%	-1.9%
Tools	51	$739,644	2.0%	6.4%	3.5%
Devices	181	$1,747,310	1.6%	4.0%	13.8%
HCIT	10	$20,426	-3.8%	-0.6%	-14.8%
Total	2035	$9,836,431	0.7%	4.3%	14.0%

Source: CapitalIQ

Number of Negative Enterprise Value Life Sciences Companies Declined in Last Week



Source: CapitalIQ

The count of negative EV life sciences companies worldwide dropped slightly to 137 from 138 last week.

We haven't seen this few negative EV companies since April 2022.

Nvidia and Lilly Stocks Now Point the Way for the U.S. Market. It's a Great Reshuffling.

Avi Salzman, *Barron's*, Mar 8, 2024 (excerpt)

The stock market's blistering run at the end of 2023 has continued in 2024. The only difference now is that there has been a changing of the guard at the top. Apple, Tesla, and Alphabet have sunk, while Nvidia and Eli Lilly are ascendant.

That makes sense. The economy is still growing— the U.S. added 275,000 new jobs in February—and companies are becoming more dynamic, too. The market is being pushed forward by real innovations in artificial intelligence and healthcare that will lead to growing cash flows years into the future. That's how investors can justify the market's higher-than-usual stock valuations.

The S&P 500 index finished the week down 0.3% after dropping 0.7% on Friday, but still notched its 16th record of 2024 the day before. The Dow Jones Industrial Average and Nasdaq Composite fell 0.9% and 1.2%, respectively, but weren't far off their own highs.

You wouldn't know it by looking at the indexes, but there's a reshuffling happening beneath the surface. Since 2018, the S&P 500 has started every year with the same four companies at the top of its market-cap leader board: Alphabet, Apple, Amazon.com, and Microsoft. Those new categories are here. Nvidia wowed investors last month when its sales results for chips powering AI applications impressed even the most bullish analysts. The stock started the year in fifth place in the S&P 500 rankings, but has now jumped to third, leaping ahead of both Amazon and Alphabet. It's less than 10% away from Apple after starting the year at less than half of Apple's valuation.

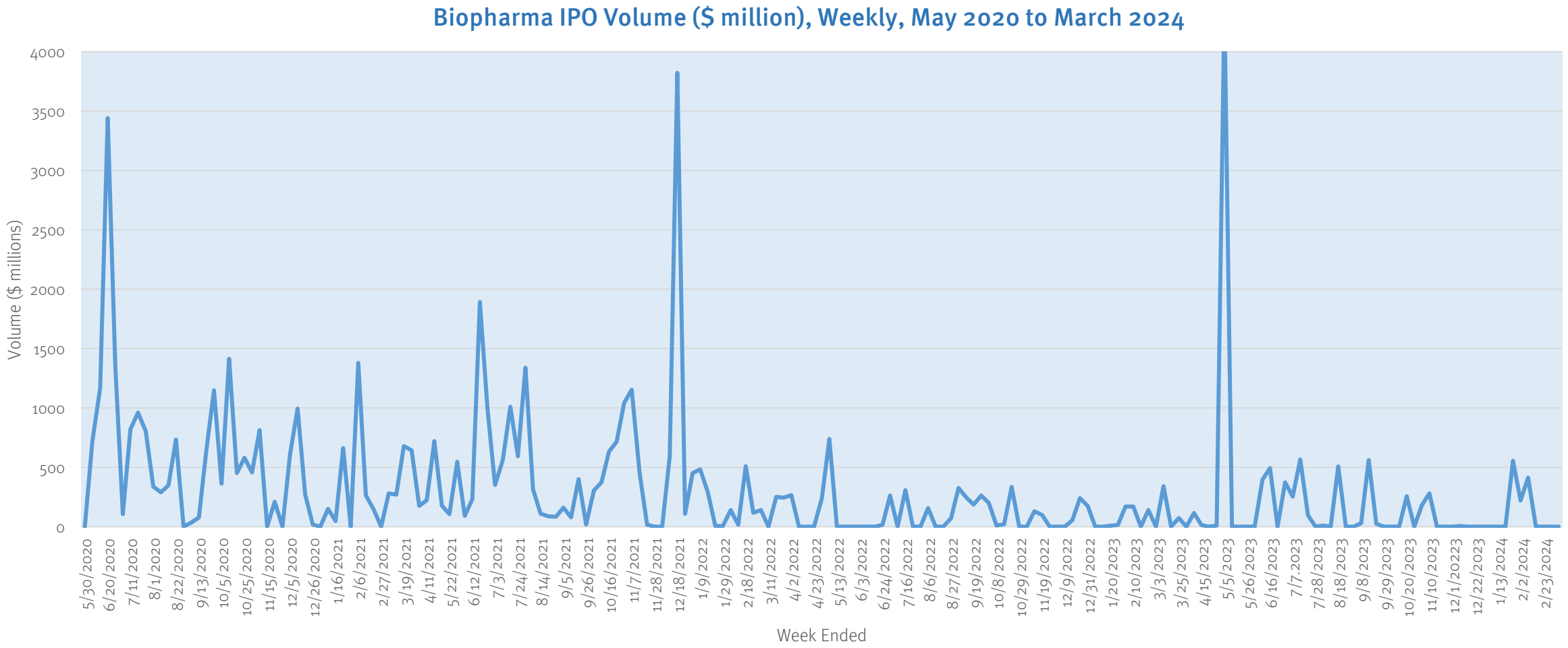
Lilly has been climbing the ranks, too, as sales projections keep rising for its diabetes drug Mounjaro. Its ascendance to eighth place in market cap has helped knock Tesla out of the top 10. The electric-vehicle maker's record of innovation has been running dry of late. It has gotten a tepid response to its Cybertruck, and has failed, at least thus far, to make a car cheap enough to compete against Chinese auto makers. Meanwhile, innovations by Lilly and rival Novo Nordisk are on the verge of remaking entire categories of healthcare. Last month, Lilly presented clinical trial results that showed its drug has a side benefit for patients with liver problems, suddenly opening up even more uses for its wonder drug.

Source: https://www.barrons.com/articles/nvidia-and-lilly-stock-now-point-the-way-for-the-market-its-a-great-reshuffling-68027afe

Capital Markets Update

IPO Market Took a Breather Last Week

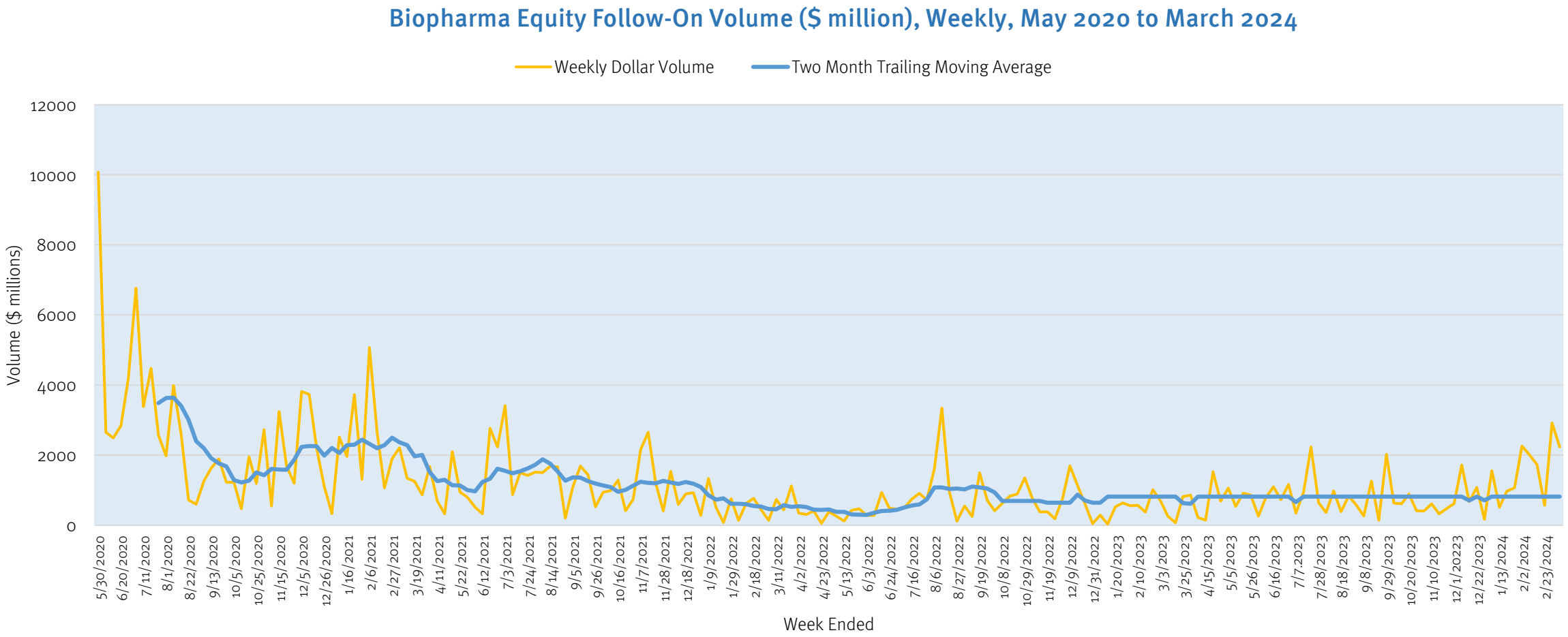
The IPO market took a break last week. We have not seen an IPO price for over a month.



Source: Data from CapitalIQ and Stifel research.

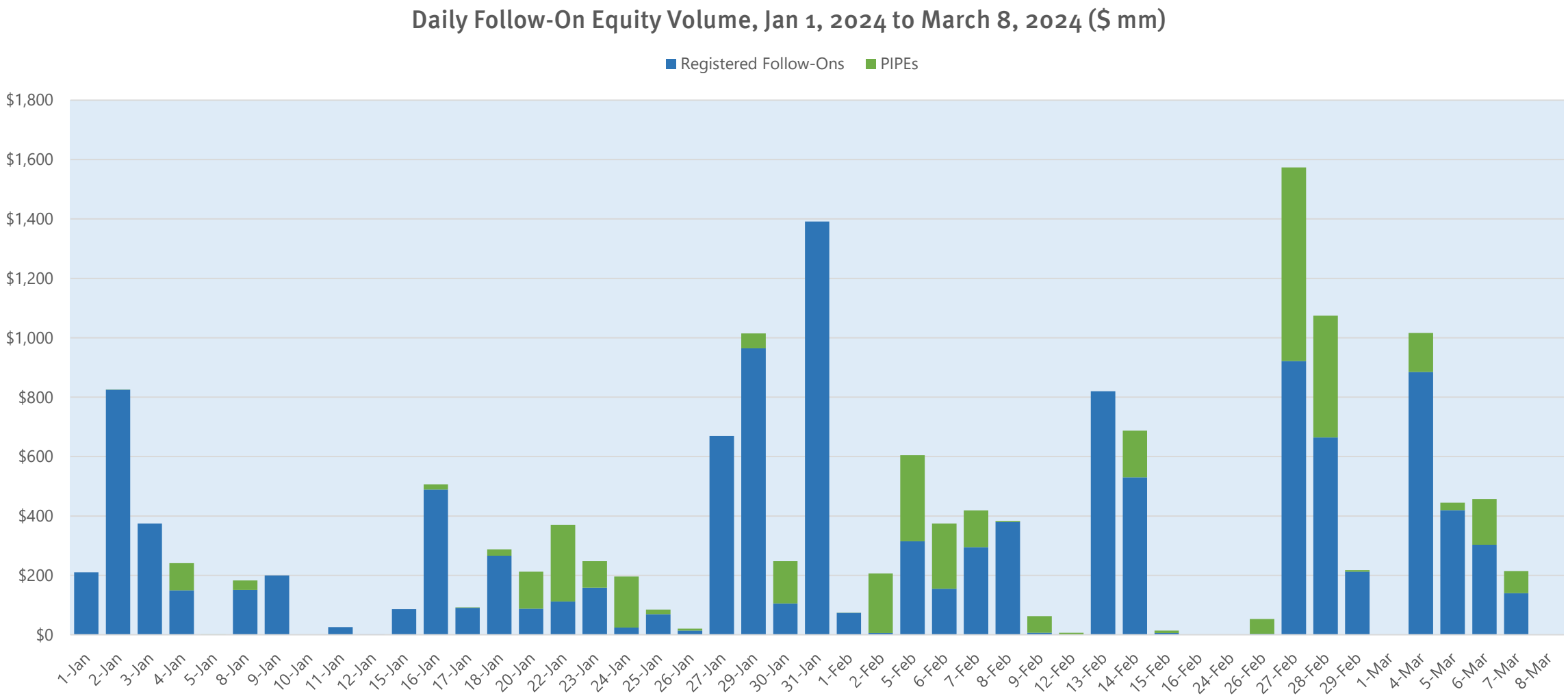
Follow-On Market Active Last Week

Last week was the third busiest of the year for follow-on offerings with $2.1 billion in deals done. In total, issuers have raised $16.2 billion in the first ten weeks of 2024 – a blistering pace by any measure.



Source: Data from CapitalIQ and Stifel research.

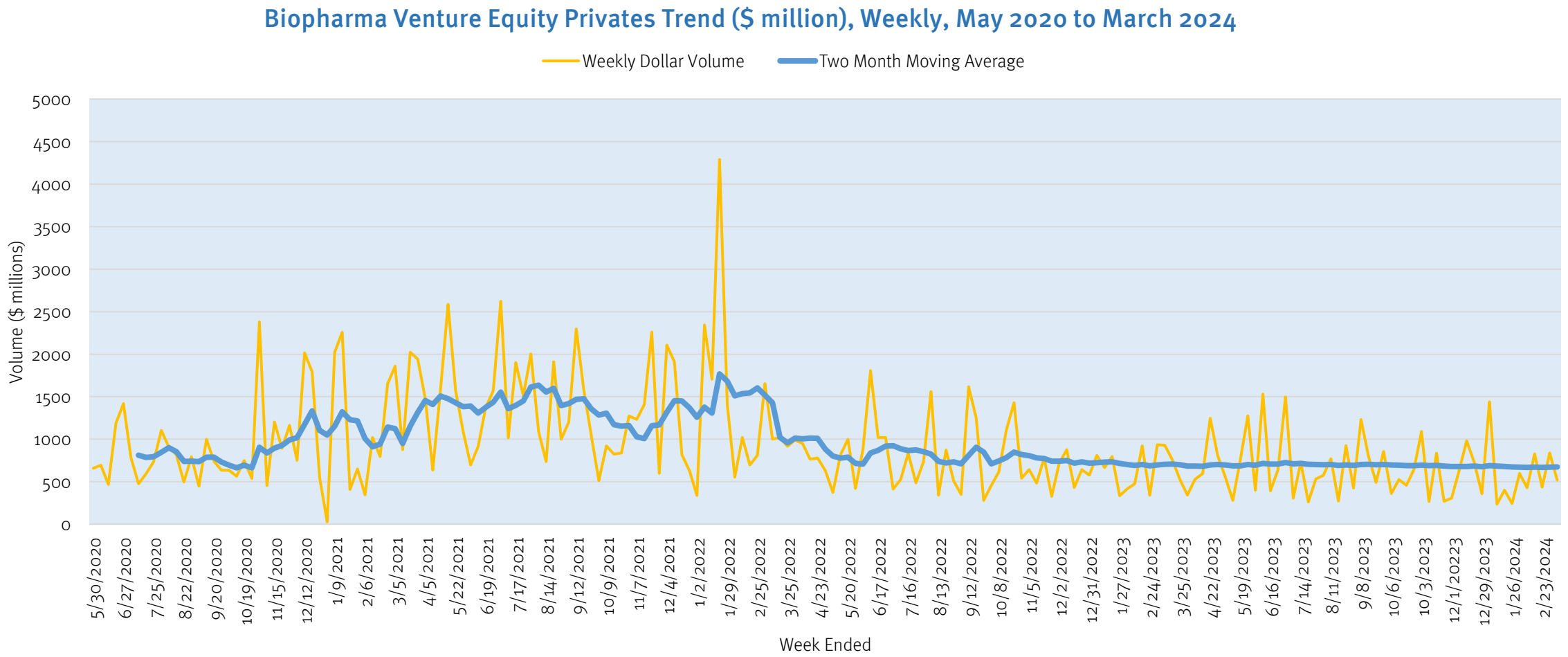
Last Week Saw Over $2 Billion in Issuance Again



Source: Data from CapitalIQ and Stifel research.

Venture Private Volume Quiet Last Week

Last week saw $519 million in privates deal volume. It was a significantly quieter week than the week before. The largest deals were raises by Alumis and Sionna.



Source: Data from CapitalIQ, Crunchbase.

Alumis Announces Upsized $259M Series C Financing to Advance Clinical-stage Pipeline in Immunology

SOUTH SAN FRANCISCO, Calif., March 6, 2024 -- Alumis Inc., a clinical-stage biopharmaceutical company developing oral therapies using a precision approach to transform the lives of patients with immune-mediated diseases, today announced an upsized $259M Series C financing. Alumis plans to use the proceeds of the financing to initiate pivotal Phase 3 clinical trials for its lead candidate ESK-001, a highly selective and potentially best-in-class allosteric tyrosine kinase 2 (TYK2) inhibitor, in moderate to severe plaque psoriasis in the second half of 2024, as well as support the two ongoing Phase 2 clinical trials for ESK-001 in systemic lupus erythematosus (SLE), and non-infectious uveitis. The financing will also support the further advancement of Alumis' precision data analytics and multi-platform approach to explore ESK-001's potential application in other autoimmune indications, as well as A-005, a TYK2 inhibitor for the treatment of neuroinflammatory and neurodegenerative diseases, and its earlier-stage internal pipeline programs.

The financing was co-led by existing investor, Foresite Capital, and new investors, Samsara BioCapital and venBio Partners, with additional participation from new investors Cormorant Asset Management, SR One, Lilly Asia Ventures, Nextech, Ally Bridge Group, HBM Healthcare Investments, Omega Funds, Piper Heartland Healthcare and existing investors AyurMaya, an affiliate of Matrix Capital Management and a U.S.-based healthcare-focused fund. Srinivas Akkaraju, M.D., Ph.D., Founder and Managing General Partner of Samsara BioCapital, and Richard Gaster, M.D., Ph.D., Managing Partner at venBio Partners, will join Alumis' Board of Directors.

Source: https://www.alumis.com/news/press-releases/030624/

"We are pleased to announce our successful Series C financing and we are grateful for the support of our strong investor syndicate, a group that shares our commitment to transforming the treatment paradigm for patients living with immune-mediated diseases. This investment will support the continued clinical development of ESK-001, building on promising data that have demonstrated full, sustained target inhibition leading to a potentially best-in-class oral TYK2 inhibitor profile."

Martin Babler
Chief Executive Officer
Alumis

Sionna Therapeutics Announces $182 Million Series C Financing to Develop Novel Small Molecules in Cystic Fibrosis

BOSTON, March 6, 2024 /PRNewswire/ -- Sionna Therapeutics, a clinical-stage life sciences company dedicated to developing highly effective and differentiated treatments for cystic fibrosis (CF), today announced the closing of a $182 million Series C financing to support the clinical development of first-in-class small molecules designed to fully restore the function of the cystic fibrosis transmembrane conductance regulator (CFTR) protein by stabilizing the first nucleotide-binding domain (NBD1).

The Series C round, which was upsized and oversubscribed, was led by Enavate Sciences with additional new investors Viking Global Investors and Perceptive Advisors, as well as participation by all existing investors including RA Capital, OrbiMed, TPG's The Rise Fund, Atlas Venture, the Cystic Fibrosis Foundation, funds and accounts advised by T. Rowe Price Associates, Inc., and Q Healthcare Holdings, LLC., a wholly owned subsidiary of QIA. Sionna also announced today that Edd Fleming, M.D., Executive Vice President of Commercialization at Enavate Sciences, is joining its Board of Directors.

CF is caused by mutations in the CFTR gene, which codes for an epithelial ion channel that is essential for producing healthy, freely flowing mucus in the airways, digestive system, and other organs. The most common mutation in CFTR, ΔF508, causes NBD1 to unfold at body temperature and severely impairs CFTR function.

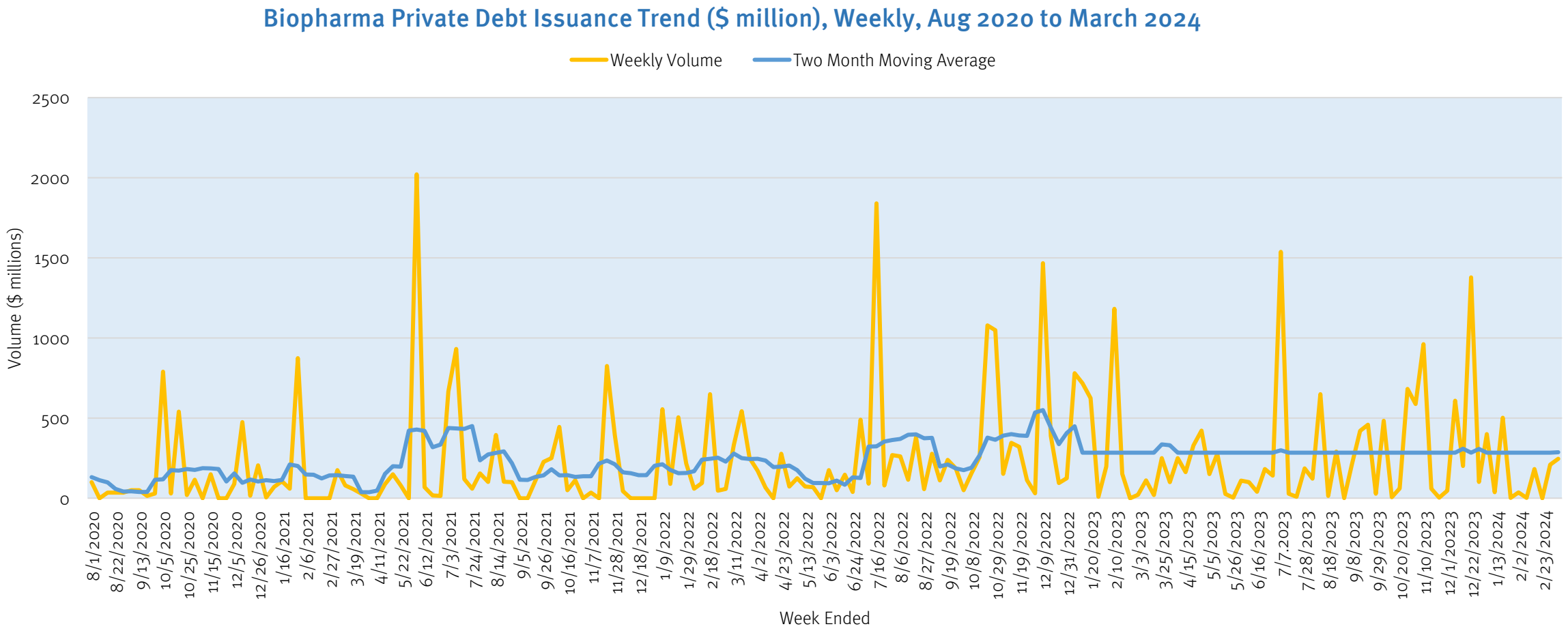
Source: https://www.prnewswire.com/news-releases/sionna-therapeutics-announces-182-million-series-c-financing-to-advance-clinical-development-of-novel-small-molecules-in-cystic-fibrosis-302080968.html

"We have deep experience in CF and a sharp focus on advancing the development of novel small molecules targeting NBD1 and complementary modulators that enable the potential for full restoration of CFTR function for most people living with CF. We are encouraged by the strong interest and validation from the excellent investors in our upsized Series C financing. This capital raise provides financial flexibility positioning us to execute our clinical development plan with funding through 2026 and multiple value-creating clinical readouts."

Mike Cloonan
Chief Executive Officer
Sionna Therapeutics

Biopharma Private Debt Placement Market Picked Up

The debt privates market picked up last week with five issuers getting their deals done. Xeris refinanced its debt with a $200mm draw from Hayfin.



Source: Data from CapitalIQ, Crunchbase.

Xeris Refinances Its $150M Senior Secured Term Loan Facility With Hayfin Capital

CHICAGO--(BUSINESS WIRE)--Mar. 6, 2024 -- Xeris Biopharma Holdings, Inc. (Nasdaq: XERS), a growth-oriented biopharmaceutical company committed to improving patients' lives by developing and commercializing innovative products across a range of therapies, today announced it has entered into an amended and restated senior secured term loan agreement ("debt facility") with funds managed by Hayfin Capital Management LLP ("Hayfin") to provide Xeris $200.0 million of capital at close and the ability to draw down another $15.2 million to redeem Xeris' outstanding 5.00% convertible senior notes due 2025.

"We are very pleased with the outcome of this refinancing transaction with Hayfin. This upsized facility, along with cash generation from our existing products and partnerships, allows us greater flexibility to continue to invest in the growth of our business. In addition to the new capital, we reduced our borrowing interest rate by 2.05% per year, which validates the strong creditworthiness of the company," said Steven M. Pieper, Xeris' Chief Financial Officer. "Hayfin has proven to be a committed partner that believes in our strategy and ability to execute and is willing to further support our growing enterprise."

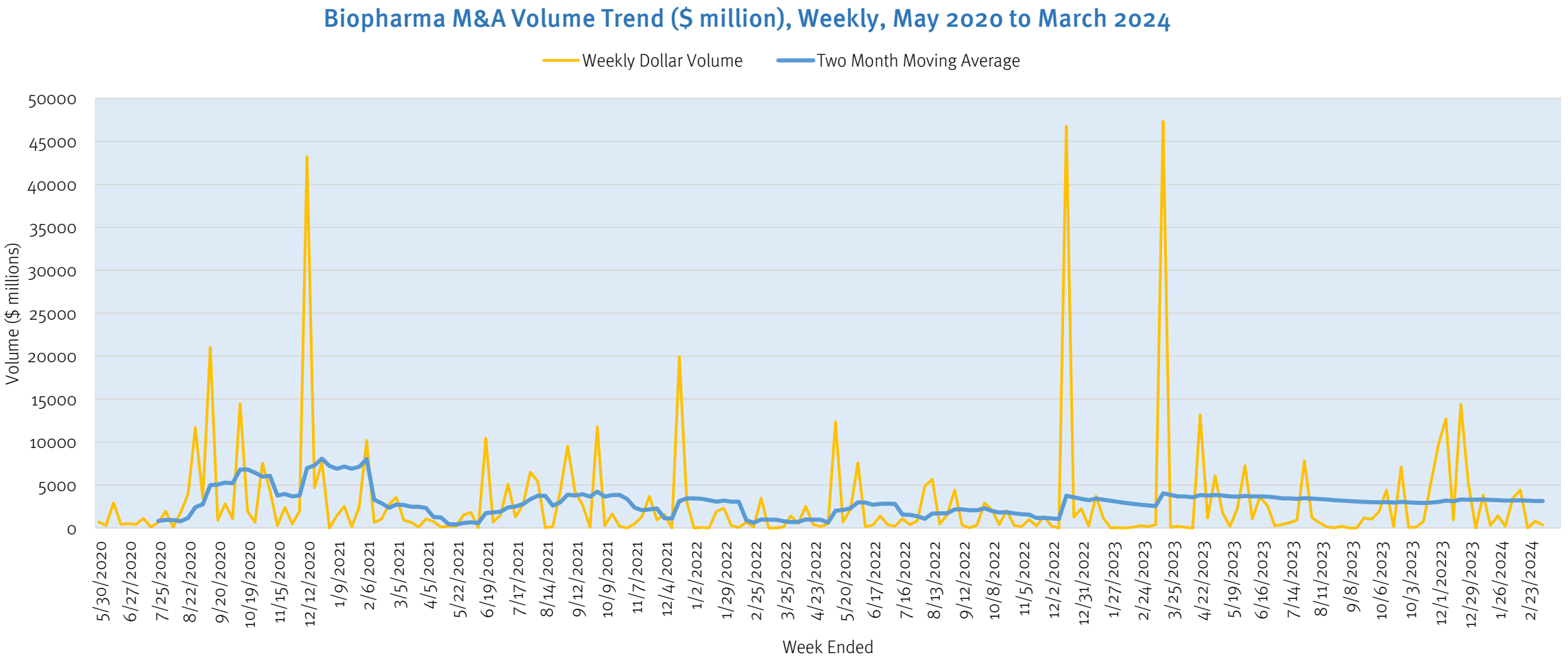
Under the terms of the new debt facility, Xeris drew down $200.0 million on the closing date to repay its existing term loan of $150.0 million with Hayfin, plus associated interest and fees, which resulted in an increase of approximately $35 million to Xeris' cash balance. Net proceeds are for working capital and general corporate purposes. An additional $15.2 million of the debt facility is available to redeem, if needed, Xeris' outstanding 5.00% convertible senior notes due mid-2025. The maturity of the debt facility is five (5) years from the closing date. Amounts borrowed under the debt facility bear interest at an annual rate equal to 6.95% plus the greater of (i) CME Term SOFR, and (ii) two percent (2.00%) per annum. Xeris is entitled to make interest-only payments on a quarterly basis until the maturity date or earlier prepayment of the loan. During the term of the loan, Xeris is required to maintain certain minimum liquidity and revenue requirements.

Source: https://xerispharma.com/news-releases/news-release-details/xeris-refinances-its-150m-senior-secured-term-loan-facility

Deals Update

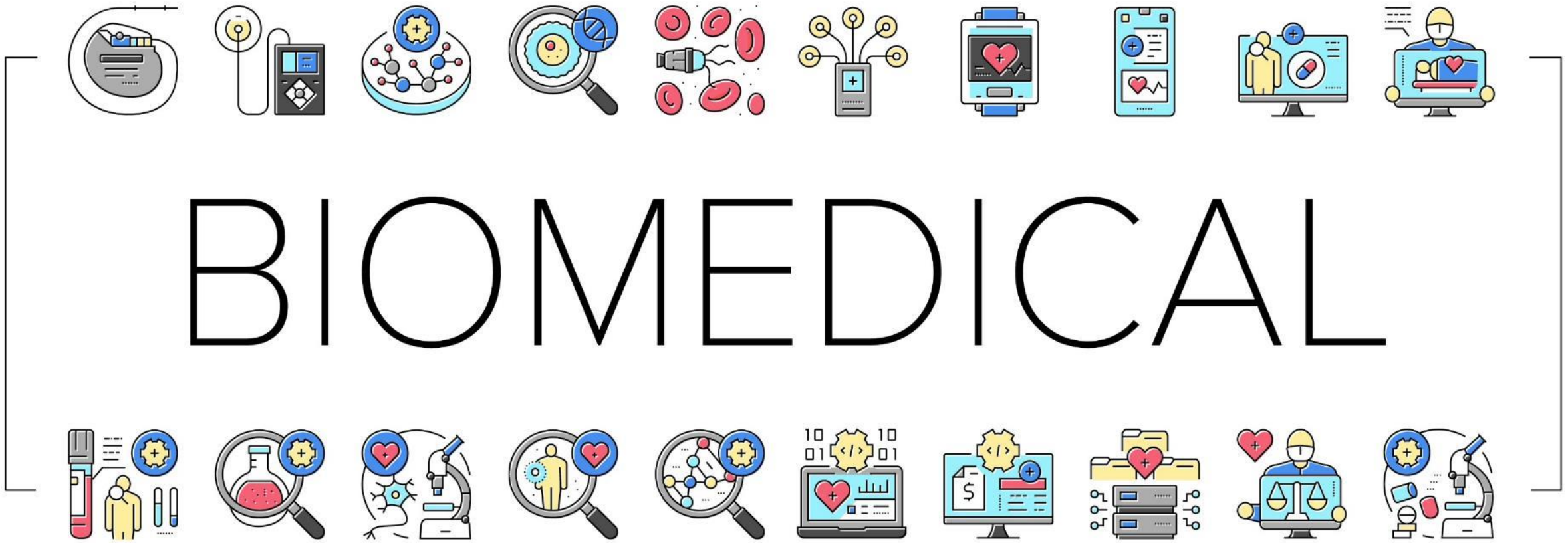
M&A Activity Modest Last Week

Last week was the third running with less than $1bn in M&A volume. There were three mergers announced including APT/BiomX, Akari/Peak and YOOV/Aptorum.



Source: S&P, CapitalIQ

Industry News



Medicare's Mental Health Care Problem

Grace McCormack, Mark Meiselbach, Josephine Rohrer, *Health Affairs*, March 4, 2024 (excerpt)

There is a growing mental health crisis among older adults: 20–30 percent of older adults older than the age of 65 report symptoms of anxiety or depression, and older adults exhibit the highest rate of suicidal ideation of any age group. However, only a fraction of affected Medicare beneficiaries receive treatment.

Recent work has uncovered critical issues with access to mental health providers in Medicare. Only 55 percent of mental health providers will see beneficiaries in traditional fee-for-service Medicare, the large government-run plan. Similarly, in the privately administered Medicare Advantage system, an estimated 65 percent of plans have narrow mental health provider networks, a rate that is substantially higher than in other privately managed insurance plans.

This lack of access to mental health providers for Medicare beneficiaries has been of increasing policy concern. The Centers for Medicare and Medicaid (CMS), Senate Finance Committee, and Biden administration have each released policy proposals to address the topic in the past year. In this article, we provide economic intuition for the unique challenges to ensuring adequate mental health care access in Medicare and evaluate recent and proposed policies to alleviate the issue.

Mental Health Providers Have Alternative Revenue Streams Apart From Medicare Patients

While for most medical specialties, Medicare provides a large share of overall patient volume, many mental health providers have alternative sources of patients.

This is driven, in part, by the overall shortage of mental health providers in the United States. More than 160 million people in the United States live in Mental Health Provider Shortage Areas—regions where the current mental health workforce is insufficient to meet the needs of the population. This shortage not only makes it difficult for traditional Medicare and Medicare Advantage to find sufficient numbers of mental health providers in many regions; it also means that many mental health providers can operate near or at capacity, even without Medicare beneficiaries.

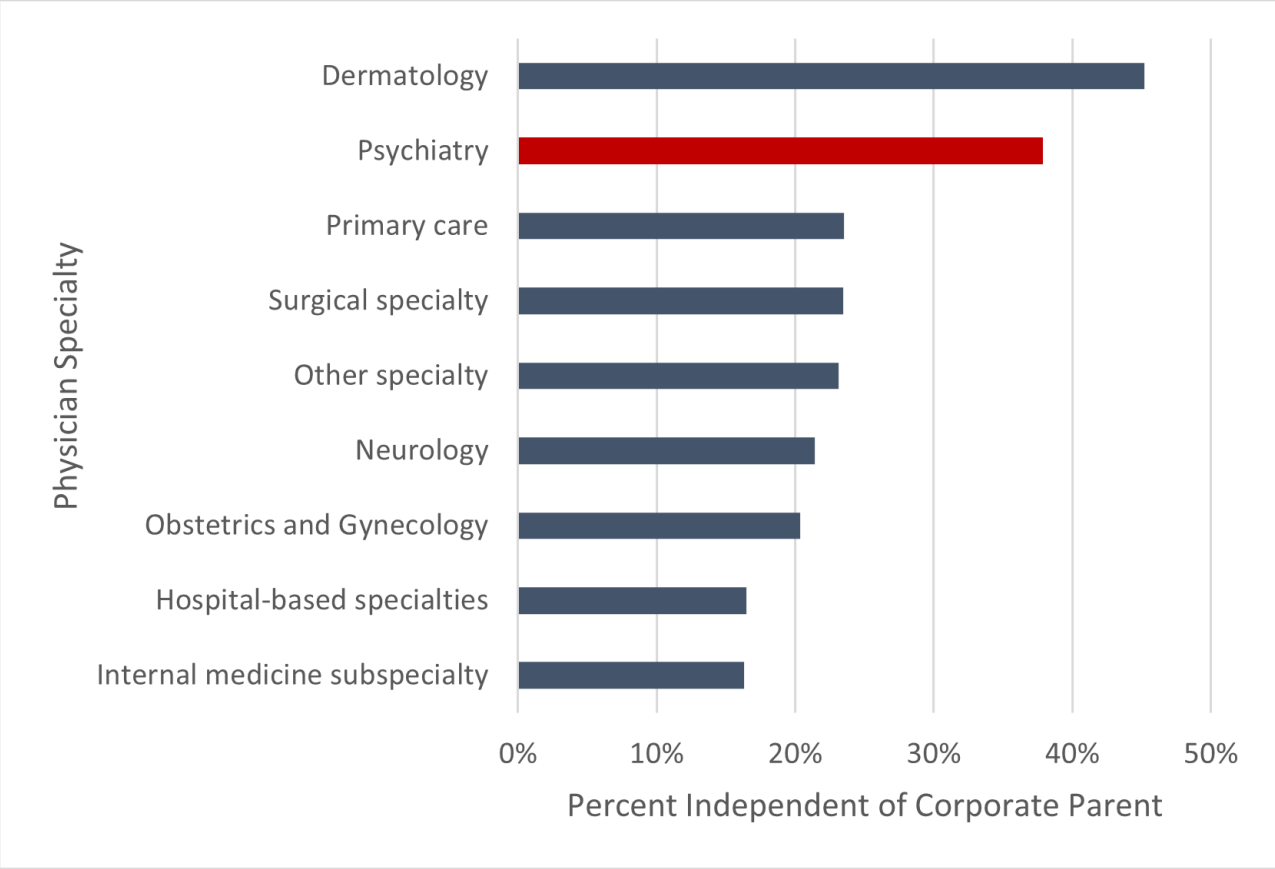
A second factor that makes Medicare a less crucial source of revenue to mental health providers, compared to other specialists, is the age of the typical mental health care patient. While many physical conditions tend to manifest in old age, mental health issues often emerge earlier in life.

Source: https://www.healthaffairs.org/content/forefront/medicare-s-mental-health-care-problem

Medicare's Mental Health Care Problem (continued)

Health Affairs, March 4, 2024 (excerpt)

Exhibit 4: Share of physicians operating independently, by specialty, 2021



Mental health providers not only have a lower incentive to participate in Medicare networks compared to other specialties, they also often have greater individual latitude in network negotiations. Often network participation decisions are made, not by individual physicians, but instead by hospital systems or medical groups, that bargain on behalf of all affiliated providers. However—by analyzing OneKey provider data on ownership status among active physicians—we show in exhibit 4, that 38 percent of psychiatrists operate independently of a larger corporate parent organization compared to 24 percent of primary care physicians. Thus, unlike other providers, whose network participation decisions are often influenced by the incentives of their corporate ownership, mental health providers can often make more tailored decisions.

Source: https://www.healthaffairs.org/content/forefront/medicare-s-mental-health-care-problem

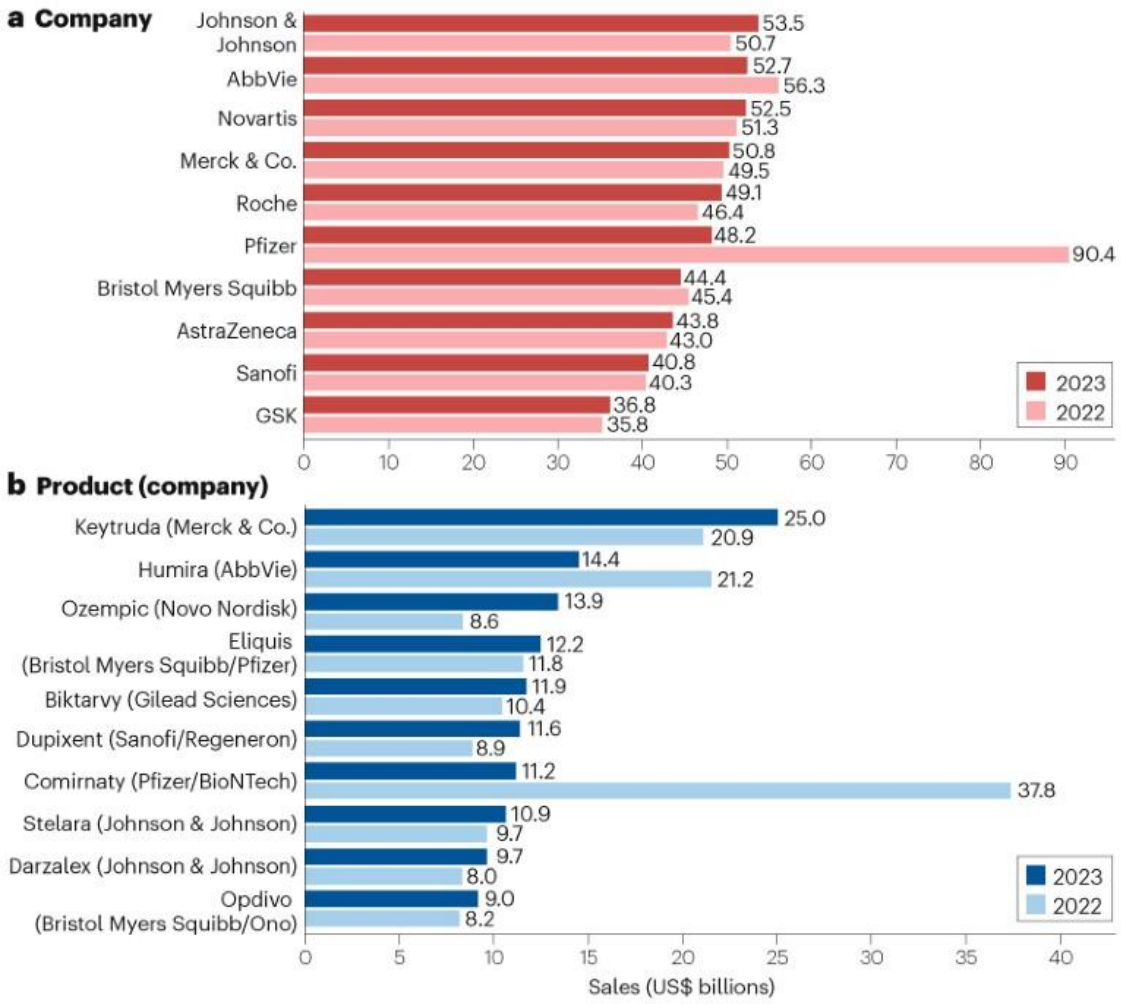
Top Companies and Drugs by Sales in 2023

Paul Verdin, *Nature Reviews Drug Discovery*, March 8, 2024 (excerpt)

Beyond movements in the company rankings, the industry can look back at 2023 as the year that Merck's Keytruda (pembrolizumab) fulfilled expectations by becoming the top-selling pharmaceutical product globally with sales of ›$25 billion, an increase of $4 billion over 2022. It is likely to hold this position for several years, with sales growth driven across a broad range of cancer settings. Indeed, Evaluate Pharma's consensus forecasts to 2028 predict that no other products will come close.

Developments in the diabetes/obesity landscape indicate it is not quite that simple, however. Another big development in 2023 was rapid growth in the glucagon-like peptide-1 (GLP-1) receptor agonist class, and in particular Novo Nordisk's semaglutide. Ozempic, one of three semaglutide-based products marketed by Novo Nordisk, was the fastest growing product in the top ten cohort in 2023. Marketed for type 2 diabetes, Ozempic sales grew by more than 60% and saw the product move from 11th to 3rd in the rankings. Taken together, Novo Nordisk's semaglutide-based franchise would technically dethrone Keytruda as early as this year based on consensus forecasts — and will propel Novo Nordisk into the top ten company rankings in the near future.

Returning to COVID-19, Pfizer's Comirnaty managed to hang on to a spot in the top ten in 2023, ranking seventh in 2023 with sales of $11.2 billion, a staggering decline of more than $26 billion from 2022. As with Stelara, this is likely to be the last time Comirnaty features in this list, with forecasts projecting a further rapid decline and flattening out of sales. Pfizer's other big COVID-19 product, the antiviral Paxlovid (nirmatrelvir and ritonavir), also declined dramatically to fall out of the top ten in 2023. Taken together, the fall in revenue from these two products compared with 2022 was ›$44 billion, driving Pfizer's slide down the rankings.



Source: https://www.nature.com/articles/d41573-024-00041-3

NYC's Bold Move: Life Sciences Take Center Stage

FierceBiotech, March 4, 2024 (excerpt)

With a bold vision and strategic investment, New York City is emerging as a global hub for the life sciences. With opportunities spanning across disease areas like oncology, cardiology, neuroscience, endocrinology, and more, NYC is proving to be a fertile ground for the development and commercialization of therapeutics, devices, vaccines, digital health tools, and sustainability solutions.

The numbers tell the story. The city's seen a 59 percent increase in life sciences employment over the past decade, with company growth quadrupling from 2019 through Q4 2023, and over 4M square feet of wet- and dry-lab space coming online. The City of New York is meeting the moment with LifeSci NYC, a $1.1B+ public investment to create 40,000 jobs, grow the city's life sciences ecosystem to 1K companies, and unlock 10M square feet of lab space. And the world has taken notice—in October 2023, Chan Zuckerberg pledged $250M, alongside a City-State $20M investment, to establish the CZ Biohub New York. The City's investment has also attracted venture capital firms who are focused on investing in disruptors in biotechnology, bioinformatics, machine learning, AI, and healthcare IT—VC firm Two Bear Capital opened its new headquarters in Manhattan last year.

What's more, advanced technologies in life sciences are entering an exciting new era powered by supercomputing, data science, AI/ML and robotics—and NYC is ready to capitalize on the technological revolution in life sciences with over 40,000 workers trained in AI and over $32B in VC funding since 2021.

NYCEDC

Source: https://www.fiercebiotech.com/sponsored/nycs-bold-move-life-sciences-take-center-stage

Amylyx's ALS treatment Relyvrio Fails PhIII Study, Biotech to Consider Withdrawing Drug

***Andrew Dunn and Max Gelman*, *Endpoints News*, March 8, 2024 (excerpt)**

Relyvrio, Amylyx's FDA-approved ALS drug, has failed a crucial Phase III trial, the company said on Friday, a major blow to what had been considered one of the few significant options available for the treatment of the deadly neurodegenerative disease.

The failure is almost certain to put access to the drug in jeopardy, and Amylyx said it would consider withdrawing the drug.

In new Phase III trial data released Friday studying 664 ALS patients, Amylyx's drug failed to outperform a placebo. The drug also missed all secondary outcomes, which included quality-of-life questionnaires, assessing the spread of the disease, and muscle function. The p-value on the trial's main goal was 0.667, a highly non-statistically significant result.

"To get the results that did not meet the primary outcome, that did not meet secondary outcomes, is both surprising and deeply saddening," Amylyx's co-CEO Justin Klee said in an interview with Endpoints News. "But at times like these, we always try to remind ourselves that as hard as it is for us, it's so much more difficult for people with ALS and their families."Amylyx's readout was one of the most anticipated biotech events of 2024. Wall Street analysts had forecasted a major swing in Amylyx's stock price based on the results, and the shares $AMLX plummeted more than 70% in premarket trading Friday morning.

Justin Klee (L) and Josh Cohen (R), Co-CEO's, Amylyx Pharma

Source: https://endpts.com/amylyxs-als-treatment-relyvrio-fails-phiii-study-biotech-to-consider-withdrawing-drug/

AbbVie Presents Lutikizumab (IL-1a/b mAb) Data in Hidradenitis Suppurativa at AAD Last Weekend

A Phase 2 Multicenter, Randomized, Double-Blind Placebo-Controlled Study to Evaluate the Safety and Efficacy of Lutikizumab in Adult Patients With Moderate to Severe Hidradenitis Suppurativa Who Have Failed Anti-TNF Therapy

Alexa B Kimball,[1] Lindsay Ackerman,[2] Hermenio Lima,[3] Tianyu Zhan,[4]
Leonidas Drogaris,[4] Ronea Chambers,[4] Mona Akbari,[4] David Williams,[4] Falk G Bechara[5]

[1]Harvard Medical School and Clinical Laboratory for Epidemiology and Applied Research in Skin, Department of Dermatology, Beth Israel Deaconess Medical Center, Boston, MA, USA; [2]Medical Dermatology Specialists, Phoenix, AZ, USA; [3]LEADER Research, Director and Associate Professor, McMaster University, Medicine Department Div. of Clinical Immunology and Allergy & Div. of Dermatology Hamilton, ON, Canada; [4]AbbVie Inc., North Chicago, Illinois, United States; [5]Department of Dermatology, Venereology and Allergology, International Centre for Hidradenitis Suppurativa/Acne Inversa (ICH), Ruhr-University Bochum, Bochum, Germany

American Academy of Dermatology (AAD 2024), 8-12 March 2024, San Diego, CA

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AbbVie Delivers Very Impressive HiSCR 50 and HiSCR75 Results

Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial

Key Eligibility Criteria:

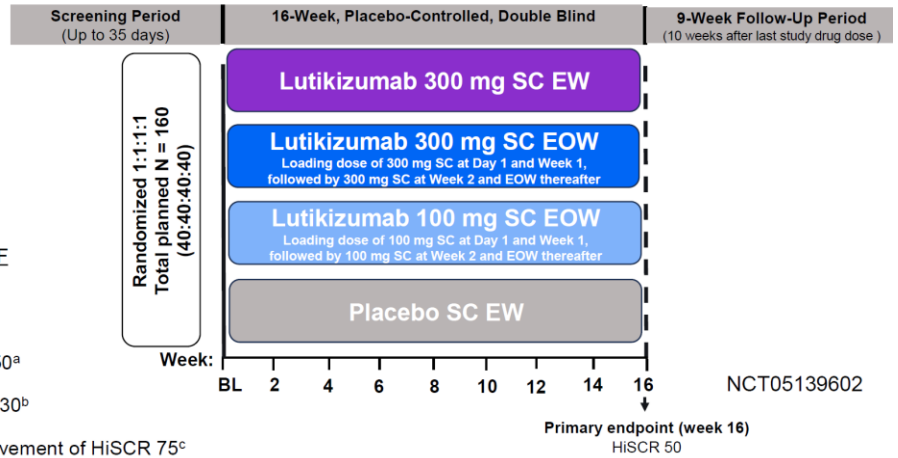
- ≥ 18 years of age at screening
- Clinical diagnosis of HS for at least 1 year prior to baseline
- Total AN count of ≥ 5 at baseline
- Presence of HS lesions in at least 2 distinct anatomic areas
- Patients must have failed anti-TNF treatment for HS

Key Endpoints:

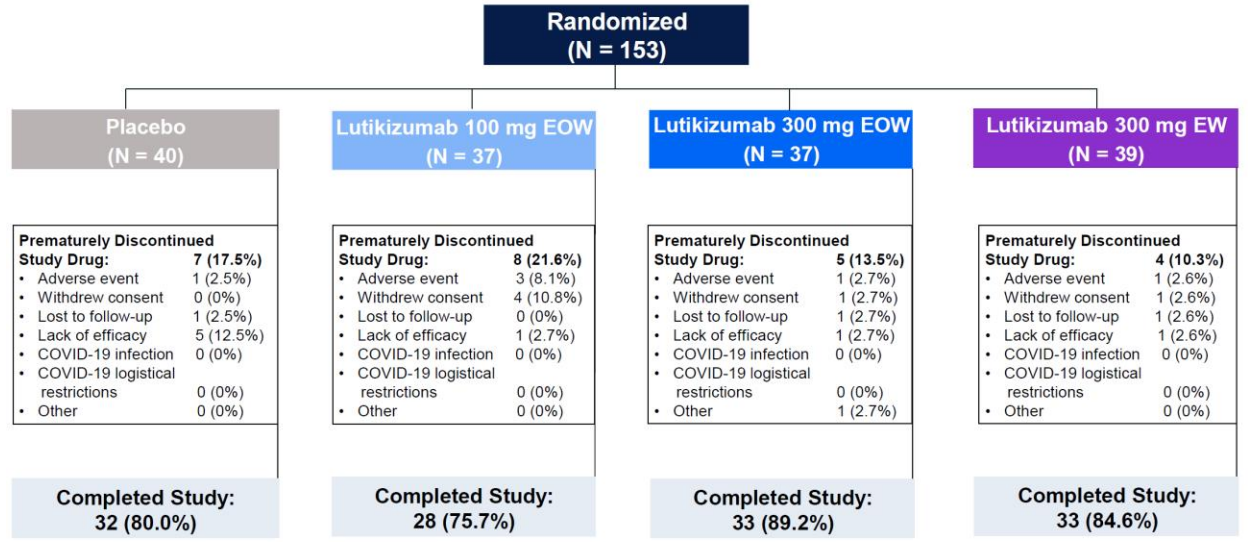
Primary: Achievement of HiSCR 50[a]

Secondary: Achievement of NRS 30[b]

Additional Key Endpoints: Achievement of HiSCR 75[c]

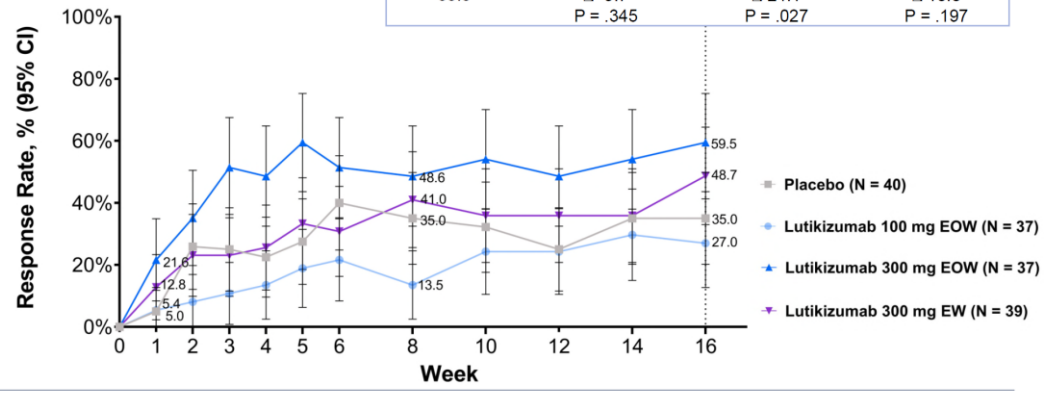


AN, abscess and inflammatory nodule; BL, baseline; EOW, every other week; EW, every week; HS, hidradenitis suppurativa; HiSCR, hidradenitis suppurativa clinical response; NRS, numeric rating scale; SC, subcutaneous; TNF, tumor necrosis factor.
The randomization was stratified by the worst Hurley Stage across all affected anatomic regions (< 3 or 3) at baseline. [a]Achievement of HiSCR 50 was defined as ≥ 50% reduction in the total AN count with no increase in abscess count and no increase in draining fistula count relative to baseline; [b]NRS30 is defined as at least 30% reduction and at least 1-unit reduction from baseline in patient's global assessment of skin pain; [c]Achievement of HiSCR 75 was defined as ≥ 75% reduction in the total AN count with no increase in abscess count and no increase in draining fistula count relative to baseline.



Patients Treated With Lutikizumab 300 mg EOW and EW Show Higher Response Rates in HiSCR 50 at Week 16 Than Those Treated With Placebo

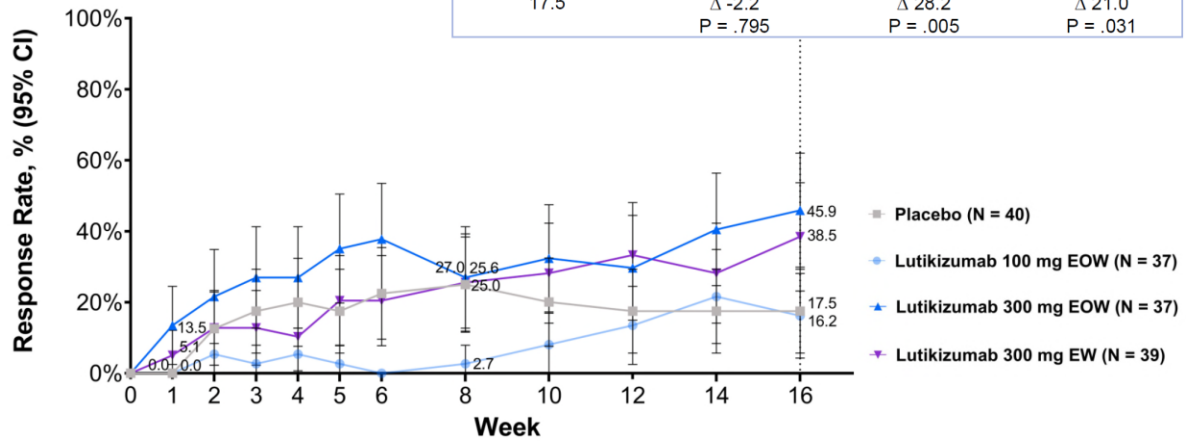
Response (%)	Response (%); Treatment Difference vs. Placebo (%)		
Placebo	Luti 100 mg EOW	Luti 300 mg EOW	Luti 300 mg EW
35.0	27.0 Δ -9.7 P = .345	59.5 Δ 24.1 P = .027	48.7 Δ 13.8 P = .197



EOW, every other week; EW, every week; HiSCR, hidradenitis suppurativa clinical response.
The proportion of patients achieving HiSCR 50 is reported using a Bayesian approach by visit and NRI-MI (non-responder imputation incorporating multiple imputation) is used to handle missing data due to COVID-19.
95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19.
HiSCR 50 is defined as at least a 50% reduction from baseline in the total abscess and inflammatory nodule (AN) count, with no increase in abscess count and no increase in draining fistula-count relative to baseline.

Patients Treated With Lutikizumab 300 mg EOW and EW Show Higher Response Rates in HiSCR 75 at Week 16 Than Those Treated With Placebo

Response (%)	Response (%); Treatment Difference vs. Placebo (%)		
Placebo	Luti 100 mg EOW	Luti 300 mg EOW	Luti 300 mg EW
17.5	16.2 Δ -2.2 P = .795	45.9 Δ 28.2 P = .005	38.5 Δ 21.0 P = .031



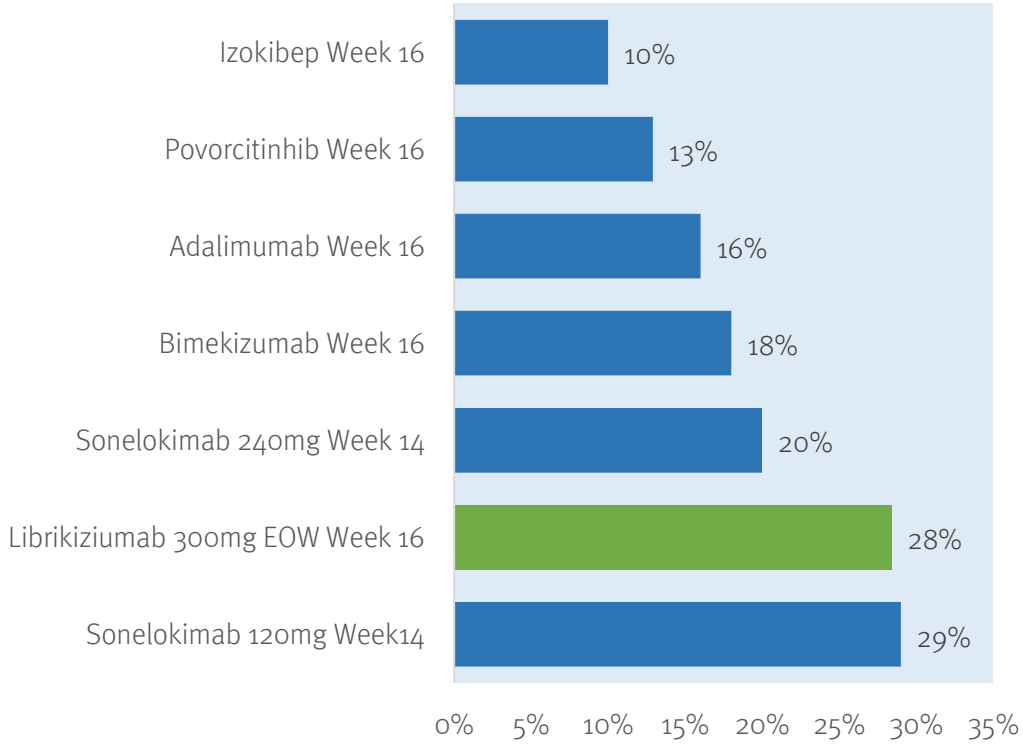
EOW, every other week; EW, every week; HiSCR, hidradenitis suppurativa clinical response.
The proportion of patients achieving HiSCR 75 is reported using a Bayesian approach by visit and NRI-MI (non-responder imputation incorporating multiple imputation) is used to handle missing data due to COVID-19.
95% CI for response rate is the synthetic result based on Student's t-distribution from PROC MIANALYZE procedure if there are missing data due to COVID-19 or is based on the normal approximation to the binomial distribution if there are no missing data due to COVID-19.
HiSCR 75 is defined as at least a 75% reduction from baseline in the total abscess and inflammatory nodule (AN) count, with no increase in abscess count and no increase in draining fistula-count relative to baseline.

Great Results in HS from AbbVie for an Anti IL-1 Antibody

AbbVie has shown that an IL-1 antibody can match the Moonlake minibody on efficacy in a population that had failed on biologics and had more severe disease at baseline. It looks to us like Moonlake will have a real competitor in the future.

1. **Deep responses**. More than half of HiSCR50 are HiSCR75 responders
2. **Clean safety**: no suicide/complementary mechanism or elevated neutropenia/infections
3. **Favorable comparison to Moonlake**: (a) Moonlake's study baseline was 14/3.5 for AN/DT count. The AbbVie Lutikizumab trial is 16.5/6 AN/DT so more severe, (b) Moonlake Hurley stage was 0/64/36 for 1/2/3, while the AbbVie Lutikizumab trial is 70% Hurley stage 3; (c) Moonlake study had 20% prior biologic experience, while the AbbVie trial featured patients with ~75% with inadequate response to prior anti-TNF therapy and 2-3 year longer duration of HS and (d) Comparable efficacy across the board.

Responder HISCR75 Difference from Placebo at Four Months in Hidradenitis Suppurativa



Source: Stifel analysis of previous HS studies.

Stuart Schreiber on Unmet Needs in Medicine

Asher Mullard, *Nature Reviews Drug Discovery*, March 1, 2024 (excerpt)

There are large unmet medical needs in a number of areas that are seemingly ready for exploration. We've picked four major areas.

The first of these is **brain health**. Genetics today shed a new light on neuropsychiatric and neurodegenerative diseases. As an illustrative example, neurodegeneration is often considered in the context of aggregating neurotoxic proteins like amyloid. But human genetics also point to different pathways that are probably upstream of these neurotoxic proteins. In the case of Alzheimer disease, it's clear that lipid metabolism and lipid transfer are involved, which is not surprising as the brain is a large reservoir of lipids.

We have also learned, over the course of the pandemic especially but also thanks to the rise of immuno-oncology, that the **immune system** has a key role in many diseases. So, there are great opportunities there.

Another focus area is **oncology**. There have been tremendous medical advances from targeted therapies, immunotherapies and more recently cell therapies like CAR T cells. But there are still major unmet needs in oncology including metastasis and drug resistance. Those are areas where the study of human biology today is providing great insight into possible medicines.

Then the fourth, and probably furthest away, is the biology of the **ageing of organs**. This area has attracted a lot of attention, and in my opinion insufficient facts and data to navigate forward effectively. But it is an area that is, I think, explosive in terms of novel insights and technologies. It’s clearly a longer-term horizon, and we are probably looking at five years to get into some of the most revealing mechanisms. But in our environment, where we can do longer-term research, it feels like an appropriate area.

Source: https://www.nature.com/articles/d41573-024-00037-z

Patients Lose Access to Weight-Loss Drugs as Employers Stop Coverage

Jennifer Calfas, *Wall Street Journal*, March 5, 2024 (excerpt)

Employers that embraced paying for weight-loss drugs are now reckoning with the high costs, forcing growing numbers to dial back or cut off their reimbursement because they can't afford it. The companies are putting in place restrictions such as limiting use to workers with high body-mass indexes, or a $20,000 cap, while others have eliminated coverage altogether. They can't sustain the spending, they say, and question whether the medications are reaching the right patients.

Jason Krynicki's health plan discontinued coverage of his Wegovy prescription Feb. 1, forcing him to tap into his retirement savings to pay for the medicine. Krynicki, a bariatric-insurance coordinator in the RWJBarnabas Health system in New Jersey, lost 47 pounds in less than a year from taking the drug. It cost him $25 a month out of pocket before his coverage ended. Now, he says, his monthly tab surpasses $1,000.

Yet use of the drugs for obesity and diabetes doubled between 2022 and 2023, and the weight-loss therapies accounted for about 2% of the university's total health-plan spending last year, said Candace Shaffer, associate vice president of benefits and payroll. The school is now considering adding restrictions, she said. One option is requiring employees to get prescriptions from the employer clinic—which also provides nutrition, wellness coaching and mental-health counseling.

"Everyone is learning as we go," Shaffer said. Weight-loss drugs such as Wegovy and Zepbound are among the hottest prescriptions in the U.S., so popular that makers Novo Nordisk and Eli Lilly can't meet demand. But the drugs list for more than $1,000 a month.

Source: https://www.wsj.com/health/healthcare/weight-loss-drugs-employer-insurance-dbe19458

Biotech VCs See Room for More Growth in Obesity Drug Market

Brian Gormley, *Wall Street Journal*, March 7, 2024 (excerpt)

Venture capitalists are financing drugmakers seeking to improve upon today's blockbuster weight-loss medications or combat their side effects. New obesity medications have helped millions of people lose weight but can cause nausea and lead to a loss of muscle as well as fat. And some people don't respond to the new treatments. Several biotechs see opportunities for novel therapies in these drawbacks.

The new drugs, such as Novo Nordisk's Wegovy and Eli Lilly's Zepbound, are injected and activate receptors for hormones, known as incretins, to suppress appetite. Biotechs are advancing oral medicines to counteract muscle loss as well as drugs that work in new ways for people who don't respond to the new obesity treatments. The growing market is complex because companies are studying many potential therapies and the future of obesity treatment may involve combinations of drugs, investors said.

"Anticipating where the puck is going is very challenging because there are so many products being developed," said Patrick Enright, a founder and managing director of biomedical investor Longitude Capital. "The category's been proven to be extremely large, so the motivation is there for any pharma that's in it to maintain their leadership," said Dr. Srinivas Akkaraju, founder and managing general partner of biotech investor Samsara BioCapital.

BioAge's drug is designed to mimic a protein the body makes more of during exercise to improve metabolism and muscle function, said Chief Executive Kristen Fortney. The company recently raised $170 million in financing led by Sofinnova Investments with participation from Longitude and other investors. The funds will support clinical trials of its drug in combination with Zepbound and other incretin drugs.

Juvena Therapeutics, similarly, is advancing its lead drug for a rare disease that causes muscle wasting, called myotonic dystrophy Type 1. The company also expects that this or a similar compound emerging from its discovery platform could be combined with an incretin to preserve muscle, said CEO Hanadie Yousef. Juvena, which raised $41 million in Series A financing in 2022, also has an earlier-stage compound that could work on its own or with an incretin to improve fat metabolism, she said. Startups Rivus Pharmaceuticals and OrsoBio seek to preserve muscle and increase weight loss through a mechanism known as mitochondrial uncoupling.

OrsoBio—whose name stems from the Italian word for bear—takes its inspiration from an observation that a bear can lose about half its body weight during its hibernation without losing lean muscle mass through mitochondrial uncoupling, in which the body burns fat without increasing activity of the energy-supplying molecule ATP, said CEO Dr. Mani Subramanian. OrsoBio, whose investors include Samsara and Longitude, is gearing up to begin midstage clinical trials in patients with obesity and metabolic dysfunction. If approved, the drug could be combined with incretin drugs, used in patients who don't respond to or can't tolerate incretins, or prescribed to patients who aim to maintain weight loss after ceasing incretin therapy, Subramanian said.

Source: https://www.wsj.com/articles/biotech-vcs-see-room-for-more-growth-in-obesity-drug-market-2af01d5a

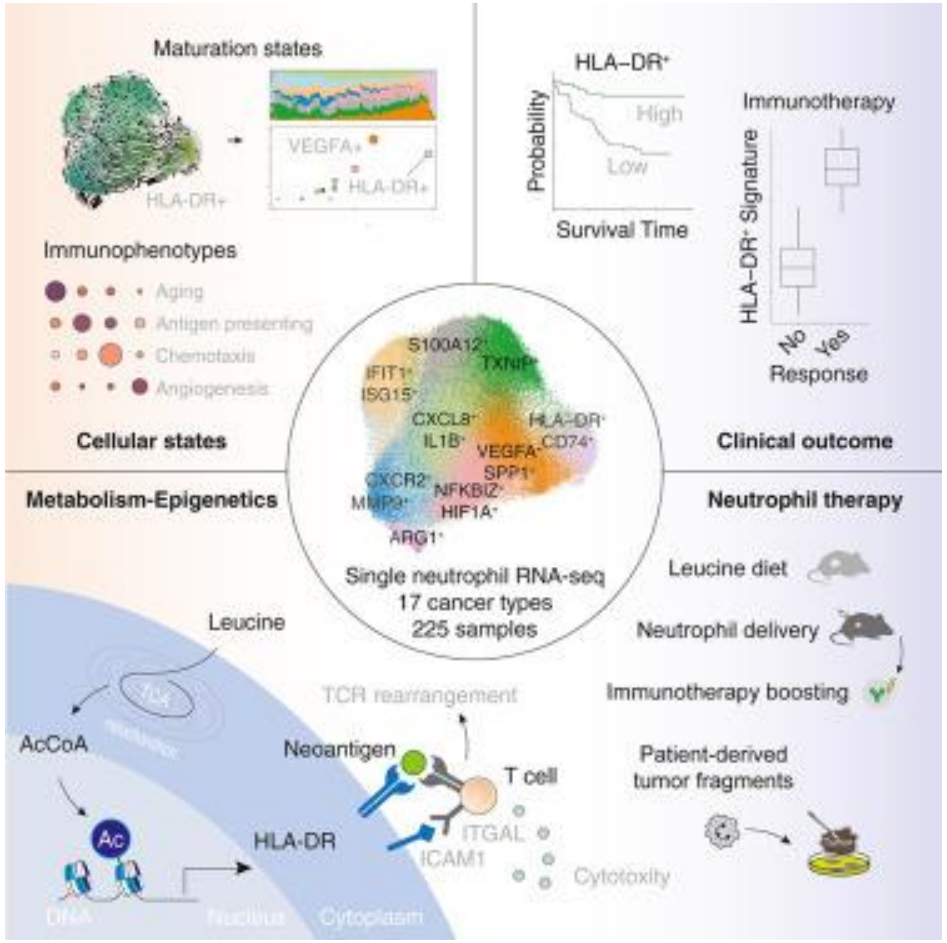
The Extraordinary Neutrophil

Yingeng Wu et.al., "Neutrophil profiling illuminates anti-tumor antigen-presenting potency," *Cell*, March 5, 2024.

Neutrophils, the most abundant and efficient defenders against pathogens, exert opposing functions across cancer types. However, given their short half-life, it remains challenging to explore how neutrophils adopt specific fates in cancer. Here, we generated and integrated single-cell neutrophil transcriptomes from 17 cancer types (225 samples from 143 patients). Neutrophils exhibited extraordinary complexity, with 10 distinct states including inflammation, angiogenesis, and antigen presentation. Notably, the antigen-presenting program was associated with favorable survival in most cancers and could be evoked by leucine metabolism and subsequent histone H3K27ac modification. These neutrophils could further invoke both (neo)antigen-specific and antigen-independent T cell responses. Neutrophil delivery or a leucine diet fine-tuned the immune balance to enhance anti-PD-1 therapy in various murine cancer models. In summary, these data not only indicate the neutrophil divergence across cancers but also suggest therapeutic opportunities such as antigen-presenting neutrophil delivery.

Source: https://www.cell.com/cell/abstract/S0092-8674(24)00126-0

This paper by a team at Fudan University looked at neutrophil behavior and fates in cancer. Extraordinarily, neutrophils adopt 10 states across cancers, demonstrating tissue and phenotype plasticity. Neutrophil maturation states span inflammation, angiogenesis, and antigen presentation.



Update on the Inflation Reduction Act

In State of the Union, Biden asks Congress to expand IRA Price Negotiation Program

Prescription Drug Pricing Comments in Biden's Mar 7, 2024 State of the Union Speech

President Biden called for an expansion of the drug pricing provisions in the Inflation Reduction Act (IRA). Specifically, he called for:

Increasing the number of drugs that could be subject to the Medicare Drug Price Negotiation Program to 50 per year (he specifically noted that he wanted Medicare to be able to negotiate 500 drugs over the next decade, which would save $200 billion). This would require Congressional approval.

Capping the cost of insulin at $35 a month for everyone regardless of their insurance. This would require Congressional approval.

Expanding the out-of-pocket cap of $2,000 per year for prescription drug costs to private insurance. This would require Congressional approval.

This is a worst-case scenario situation on IRA. Expansion of the number of drugs covered per year in the IRA to 50 would be quite negative for the pharmaceutical industry.

Legal Challenges To IRA Drug Price Negotiations Face Skeptical Judges

Joshua Cohen, *Forbes*, Mar 9, 2024 (excerpt)

A district court judge in New Jersey heard oral arguments this week with respect to claims brought forth by four pharmaceutical companies that the Inflation Reduction Act's drug price negotiation provision violates certain constitutional rights. According to Law360, the judge presiding over the case appeared "particularly doubtful about the companies' position that the negotiation program amounted to an unconstitutional taking of their property." Further, Endpoints News noted that the judge seemed "skeptical" of the plaintiffs' arguments that participation in the program was not voluntary.

Legal challenges to the Medicare drug price negotiation provision contained in the IRA have thus far faced skeptical judges. The overarching theme of the court dismissals has been that negotiated prices for drugs cannot be considered confiscatory because drug makers who do not wish to participate Medicare can opt out. This implies, according to the judges involved in recent court decisions, that there is no legally protected right to sell products to the government at market rate prices, regardless of how important this may be from a business perspective. By extension, consequences connected to engaging with the government, such as lower prices of the goods being sold, can't be considered a constitutional violation.

Earlier this month, a federal judge in Delaware ruled against AstraZeneca's complaint that sought to halt ongoing negotiations of the price of its diabetes drug, Farxiga (dapagliflozin).

Source: https://www.forbes.com/sites/joshuacohen/2024/03/09/legal-challenges-to-ira-drug-price-negotiations-face-skeptical-judges

Venture Capital and the IRA

Matthew Vogel, Rena Conti & Amitabh Chandra, "Biopharma Venture Capital And The Inflation Reduction Act," *Health Affairs*, March 5, 2024 (excerpt)

The Inflation Reduction Act (IRA) of 2022 is the most significant reform to US prescription drug pricing in two decades and the first expected to result in a net reduction in Medicare drug costs. Although beneficial for today's payers and patients, the magnitude of the law's effect on future innovation is disputed. The Congressional Budget Office (CBO) estimated that the IRA will result in a decrease of one new drug in the first decade and an additional 12 drugs over the following two decades. An industry-sponsored study warned of a decrease of 139 drugs in the first decade alone. With the law now well into its implementation, assumption-driven forecast models should increasingly give way to contemporary empirical evidence. If the IRA is as consequential as its supporters and detractors contend, evidence of its effects may already be emerging.

Academic studies of previous shocks affecting drug development used systematic measures, such as changes in the number of new drug approvals and indications, company research and development (R&D) spending, and the composition of product pipelines and clinical trials. However, interpretation of these changes requires caution. One challenge to studying policy's potential impact on innovation is the lag effect of the decade-long drug development process.

We followed up on our recent analysis of the impact of the IRA on pharmaceutical company revenues by focusing on biopharma venture capital (VC) funding. VC is a key driver of innovation, with VC-backed emerging biopharma companies originating more than half of all new drug approvals. It is reasonable to speculate that changes in funding or valuations for early-stage companies in 2022 or 2023 could be leading indicators of IRA-related changes in the broader pharmaceutical innovation ecosystem. We provide some evidence of these changes related to the IRA and place them in broader context.

During the COVID-19-era, biopharma VC funding underwent a substantial expansion, more than doubling from 2019 to 2021 (exhibit 1). In 2022, however, funding decreased by 22 percent followed by another 28 percent in 2023. Industry observers disagree on how to contextualize these changes. They can be described, with equal accuracy, as either ominous consecutive decreases or more mundane mean reversion to the pre-pandemic growth trajectory. Some may view the decreases as vindicating predictions that the IRA would result in a plunge in VC investment, but the decline in funding began before the text of the legislation was released in July 2022 and occurred against the background of multiple material upheavals: a marked rise in inflation expectations and interest rates, "risk-off" investor sentiment, and the popping of the COVID-19-era bubble.

Source: https://www.healthaffairs.org/content/forefront/biopharma-venture-capital-and-inflation-reduction-act

Biopharma Venture Capital And The Inflation Reduction Act

Vogel, Conti and Chandra (VCC) study (continued)

Exhibit 1 also illustrates recent increases in the biopharma share of total VC funding since 2021 (see the red dashed line). Given that biopharma funding declined in 2022 and 2023, the industry's growing share of overall VC funding during that period is a function of larger decreases in non-biopharma VC funding. Indeed, biopharma's 28 percent decrease in VC funding in 2023 was smaller than the 31 percent decrease in overall VC funding (not shown), including a 34 percent decrease in funding for the rest of the health care sector (for example, devices, services, and information technology). These data suggest that economywide shocks provide a more compelling explanation for recent changes in biopharma funding than the IRA.

Our result is consistent with a December 2023 CBO analysis that found "no evidence of a systematic decrease in the percentage of venture capital flowing to pharmaceutical companies after August 2022—or in the period immediately preceding the law's enactment." Our analysis differs from the CBO's in that our data did not show that biopharma's share of overall VC funding reached a historic high in 2023. It is unclear if this discrepancy is because of differences in the composition of the underlying data sets or noise. Rather, we found the 2023 biopharma funding share was at its 10-year average of 13 percent of all VC funding and 51 percent of health care VC funding (not shown) and that it tracked changes in the rest of health care (see blue dashed line in Exhibit 1) and other VC-funded sectors as it has historically.

Source: https://www.healthaffairs.org/content/forefront/biopharma-venture-capital-and-inflation-reduction-act

Exhibit 1

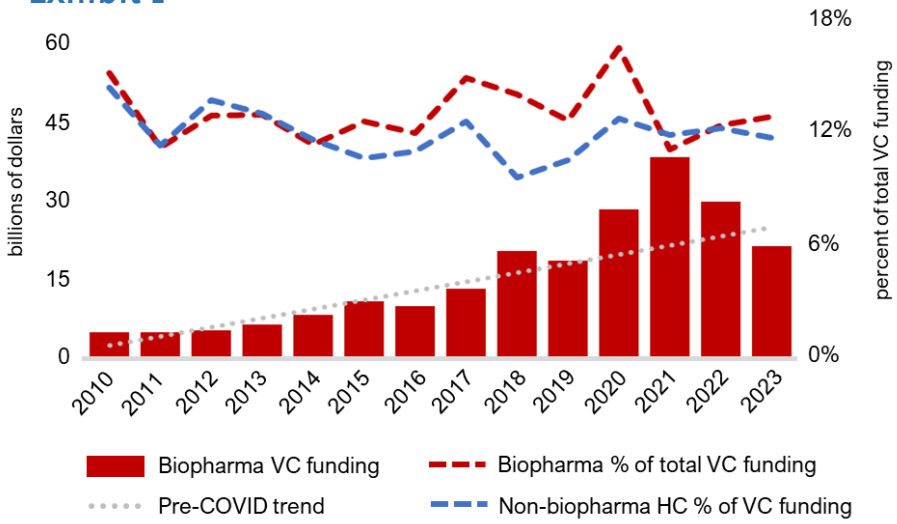
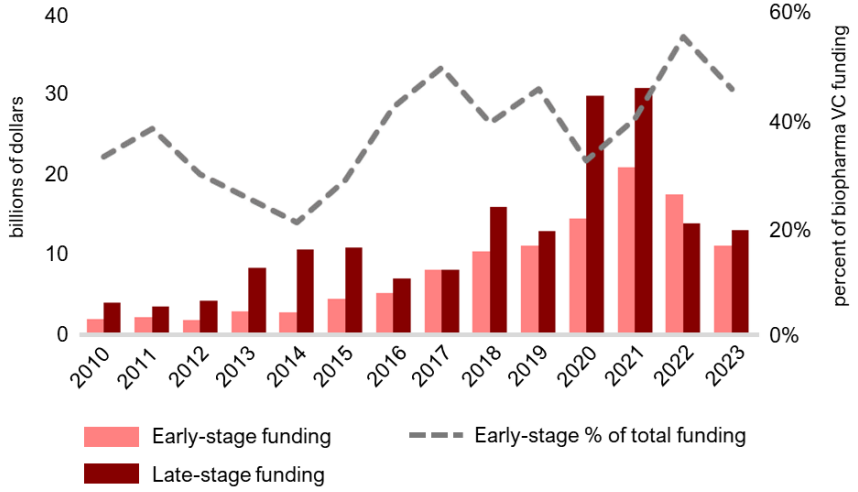


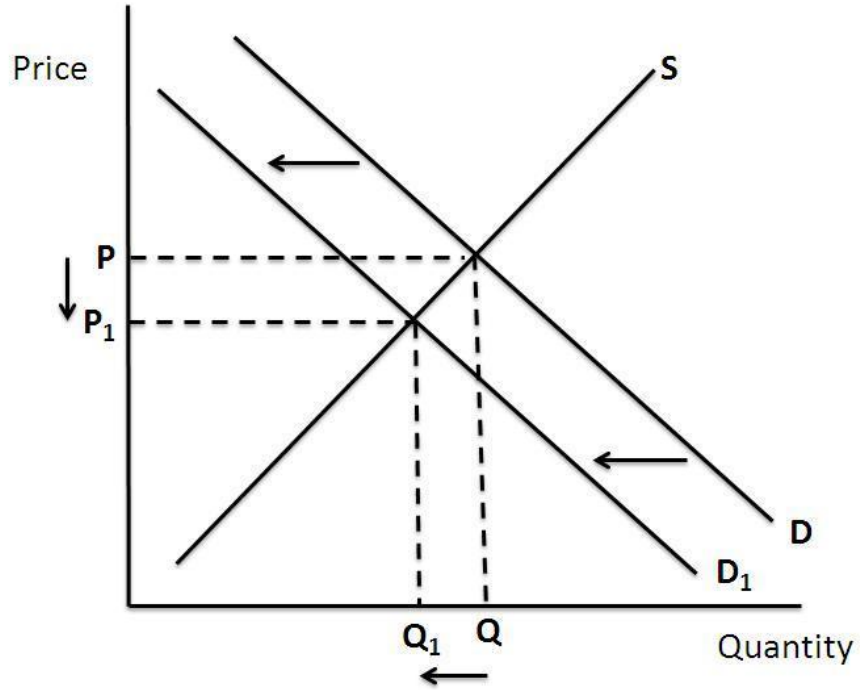
Exhibit 2



Issues With The VCC Study

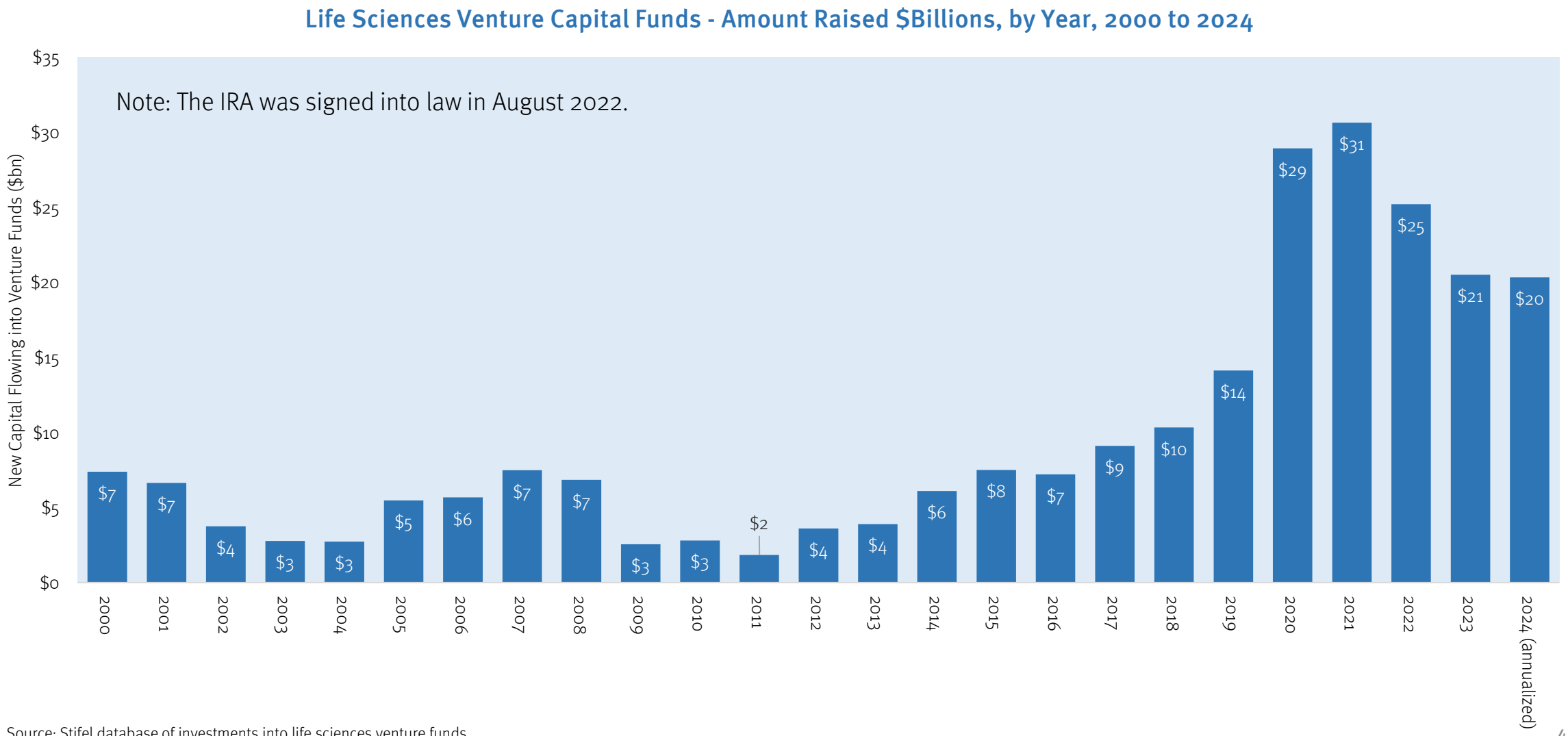
1. VC incentives are not as tied to prospective returns as one might guess. VC's do get carried interest when they make great investments, but they also get paid management fees for putting money to work.
2. It's not at all obvious that the CBO / VCC idea of seeing whether more money is put to work in biopharma is the right way to measure the impact of the IRA on investment returns.
3. Most economists would note that looking at changes in quantity of a product sold would not in any way provide evidence of a shift in demand for the product. As shown at right, changes in quantity of a product could reflect changes in the supply curve for that product, for example.
4. We'd suggest that there are better ways of getting at the underlying question:
    a) Asking large allocators of capital in the sector (e.g., pharma companies) if they are changing their behavior. You don't have to guess by looking at murky data. You can just ask.
    b) Looking at how pharma companies are allocating R&D dollars. Are they putting more into small molecules versus large molecules?
    c) Looking at LP behavior. Unlike GP's, LP's do not get management fees and so are much more sensitized to prospective returns in a sector. Their behavior should tell us how they are thinking.

S=supply, D=Demand, Q=Quantity



In classic economic theory, a drop in demand for a good would cause the quantity sold and the price of sale to drop. However, this assumes that all else, including supply, is equal. In the real world, all else is rarely equal. Paradoxically, the VCC study, prepared by at least one professional economist, assumes otherwise.

LP Dollars Flowing to Venture Funds Dropped Substantially After Passage of IRA



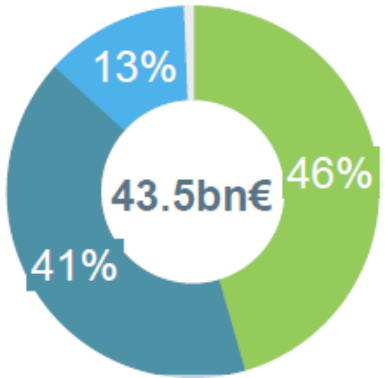
Source: Stifel database of investments into life sciences venture funds.

Bayer Investor Day (Mar 5, 2024)

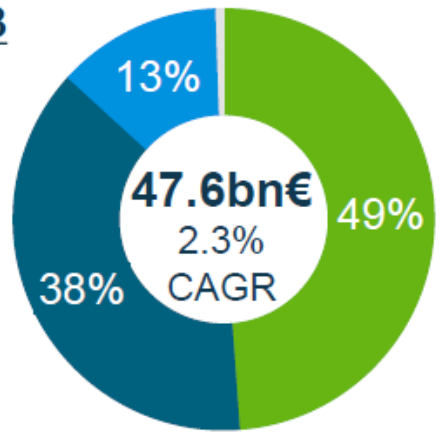
Bayer: A Global Leader in Health & Nutrition

Net Sales *as rep*[1]

2019



2023



Crop Science

- #1 in Seed & Traits with Leading Crop Protection Portfolio
- >200 bn€[2] exp. Global Ag Input Market & Related Adjacencies by 2030

Pharmaceuticals

- Strong market positions in key therapeutic areas / resilient base
- Rebuilding R&D with technology platforms and improved productivity

Consumer Health

- Iconic brands with leading market positions
- 3-5% CAGR CH Global Market[3]

Well Positioned in Growing Markets

to address

Major Societal Needs and Ecological Challenges

with the

Power of Innovation.

Health for All, Hunger for None.

[1] As rep = as reported, Animal Health business not included, Environmental Science Professional business included in figures until sale completion in 2022 (no restatement)
[2] Company estimates; [3] Outlook, internal market model in-market sales OTC medicines, data from IQVIA, Nicholas Hall

What I‘ve found at Bayer

Strong *FOUNDATION* that can drive a prosperous future …

- Importance of the Mission
- Science and Innovation
- Leading Positions in Crop and Consumer
- Rebuilding Pharma Business
- Skilled and Dedicated Workforce

… but *FOUR* major challenges that need to be addressed

- Pharma LoE, Pipeline Structure
- Litigation
- High Debt
- Bureaucracy

Bayer Taking Decisive Action and Making Changes

ACTION

- Initiated operating model overhaul
- Proposed temporary minimum dividend
- Delivered adjusted guidance

CHANGES

- Proposed Supervisory Board refresh
- Proposed change to management compensation
- Changing guidance approach

Strengthening accountability and transparency across the company

EXAMPLARY

Strong Momentum in Scale Up, with Numerous Initiatives Globally

< 50 Customer and Product Teams at end of 2023

~ 300 in March 2024

By end of 2024, we will have started in every part of Bayer working in the new operating model.

North & Latin America

// **PH US:** More versatile and agile organization with decision power at the customer

// **CS US:** First deployment of new customer-centric teams in Illinois and Wisconsin

// **CH US:** "One-A-Day" team (Nutritionals) as early adopters

~200 Customer & Product Teams now running

Europe, Middle East & Africa[1]

// **PH Global:** Accelerate launch for Eylea 8mg

// **CS Romania:** Launched new customer-centric teams

// **PH Product Supply API**: More targeted, agile & competitive set-up

~60 Customer & Product Teams now running

Asia-Pacific

// **CH ASEAN:** Accelerate innovation cycles

// **PH Japan**: Dynamic budgeting by teams

// **CS Western India:** First deployment of new customer-centric teams

~40 Customer & Product Teams now running

Status: As of March 1st, 2024
1 Includes global initiatives

Through 2026: Enhance Performance and Regain Flexibility

GROUP	CROP SCIENCE	PHARMA	CONSUMER HEALTH
Implement **dynamic shared ownership** to improve performance and fuel growth	Outgrow market in core business	Support topline resilience during LoE's of major products	Grow above market
Strengthen cash flow	Improve profitability	Drive productivity gains to support margins	Deliver profitability at industry competitive margin level
Improve towards single A category rating	Extend innovation leadership with annual portfolio refresh and advancement of blockbuster technologies	Advance early assets to re-create promising mid-/late pipeline	Further build our iconic brands through innovation and commercial excellence
Advance strategies to **contain litigation**			

Pharmaceuticals – Pipeline Overview[1] (as of Feb 20, 2024)

Phase I

- HER2/mEGFR Inhibitor *(BAY 2927088)*
- DGKzeta Inhibitor *(BAY 2965501)*
- CCR8 Ab *(BAY 3375968)*
- VVD KEAP1 Act *(VVD-130037 aka NRF2 Inh, BAY 3605349)*
- DGKalpha Inh *(BAY 2862789)*
- PSMA TAC *(BAY 3546828)*
- VVD STAT3 Inhibitor *(VVD-130850, BAY 3630914)*
- sGC Activator Oral *(BAY 3283142)*
- SEMA 3a *(BAY 3401016)*
- Anti-coagulant *(BAY 3389934)*
- Bemdaneprocel (Parkinson's Disease Cell Therapy) *(BRT-DA01)*
- Parkinson's Disease rAAV Gene Therapy *(AB-1005 aka AAV2-GDNF-PD)*
- Multiple System Atrophy rAAV Gene Therapy *(AB-1005 aka AAV2-GDNF-MSA)*
- Pompe Disease rAAV Gene Therapy *(ACTUS-101)*
- Huntington's Disease rAAV Gene Therapy *(AB-1001 aka BV-101)*
- LGMD2I/R9 rAAV Gene Therapy *(AB-1003 aka LION-101)*
- GPR84 Antagonist *(BAY 3178275)*
- BAY 2701250

Phase II

- Congestive Heart Failure rAAV Gene Therapy *(AB-1002)*
  - // Congestive Heart Failure (GenePHIT)
- Anti-a2AP *(BAY 3018250)*
  - // Acute Ischemic Stroke; Pulmonary Embolism (SIRIUS)
- Zabedosertib (IRAK4 Inh.) *(BAY 1834845)*
  - // Atopic Dermatitis (DAMASK)
- Runcaciguat (sGC Activator) *(BAY 1101042)*
  - // Non-prolif. Diabetic Retinopathy (NPDR) (NEON-NPDR)

Phase III

- Darolutamide (AR Inhibitor)
  - // Prostate Cancer (mHSPC) (ARANOTE)
  - // Adjuvant Prostate Cancer (DASL-HiCaP)
  - // Prostate Cancer with Biochemical Recurrence after Curative Radiotherapy (ARASTEP)
- Finerenone (MR Antagonist)
  - // Heart Failure (HFmr/pEF) (FINEARTS-HF)
  - // Non-diabetic CKD (FIND-CKD)
- Vericiguat (sGC Stimulator)
  - // Heart Failure (HFrEF) (VICTOR[2])
- Asundexian (FXIa Inhibitor)
  - // 2° Stroke Prevention (OCEANIC-STROKE)
- Elinzanetant (Neurokinin-1,3 Rec Antagonist)
  - // Vasomotor Symptoms (OASIS)
- Aflibercept 8mg (VEGF Inhibitor)
  - // Retinal Vein Occlusion (QUASAR)
- Gadoquatrane (High Relaxivity Contrast Agent)
  - // Magnetic Resonance Imaging (QUANTI-CNS, QUANTI-OBR)

Submissions

- Aflibercept 8mg (VEGF-Inhibitor)
  - // CN: Neovasc. Age-rel. Macular Degen. (nAMD)

Oncology
Cardiovascular+[3]
Neurology & Rare Diseases
Immunology
Others

New molecular entity
Life cycle management

Full pipeline package available for download under:
https://www.bayer.com/en/pharma/development-pipeline

Protein Therapeutics | Cell Therapy | Contrast Agent | Genetic Medicine | Radionuclide Therapy | Small Molecule

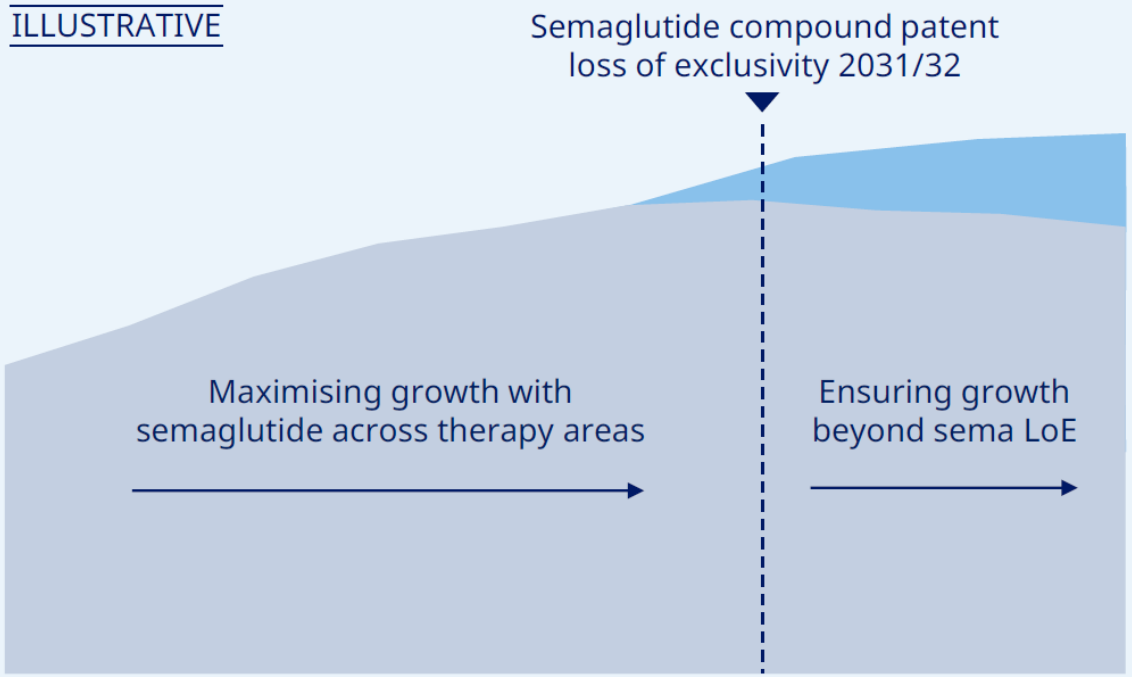
[1] Bayer and partner sponsored + 3rd party label enabling studies with first patient first visit
[2] Conducted by Merck & Co [3] Including Precision Cardiovascular, Nephrology & Acute Care

Novo Nordisk Capital Markets Day

Building for future growth from a position of strength

Growth beyond semaglutide loss of exclusivity remains a key priority

ILLUSTRATIVE



Corporate strategic focus areas

- Expand and progress R&D pipeline
- Expand manufacturing capacity
- Evolve organisation to support sustained innovation and growth

LoE: Loss of exclusivity; Sema: Semaglutide

Translation from corporate strategic priorities to R&D pipeline

	Diabetes	Obesity	Cardiovascular disease	Rare blood disorders
Near-term focus	Maximise CagriSema Maximise insulin icodec Progress projects in core biologies	Maximise CagriSema Progress projects in core biologies Pursue new MoAs	Maximise ziltivekimab Strengthen pipeline through internal and external candidates	Maximise Mim8 Maximise etavopivat
Long-term focus	Pursue disease modification Pursue transformational insulin	Pursue disease modification MoAs to go beyond traditional weight loss	Pursue new MoAs Pursue disease modification	Focus on transformative and curative approaches

MoA: Mechanism of Action

CMD24 CAPITAL MARKETS DAY

siRNA platform expected to deliver and mature across therapy areas in alignment with corporate strategy

Progress with the siRNA platform

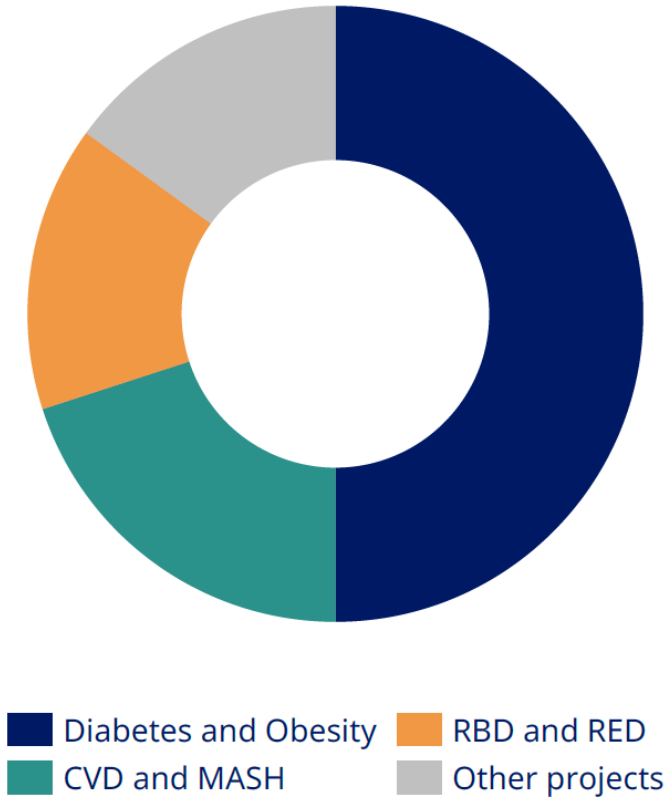
11 phase 1 trial initiations with GalXC™ since 2017

Rivfloza™ the first Novo Nordisk siRNA drug, approved in 2023

First extra-hepatic phase 1 trial with GalXC-Plus™ in 2023

50% of upcoming phase 1 trials expected to be with GalXC-Plus™

Distribution of siRNA portfolio projects



Phase 1 initiation ambition with siRNA

3

… phase 1 initiations on average per year across disease areas with the siRNA platform is **on track**

CVD: Cardiovascular disease; MASH: Metabolic dysfunction-associated steatohepatitis; RBD: Rare blood disorders; RED: Rare endocrine disorders; siRNA: Small interfering ribonucleic acid
Note: A project is defined when a target is identified and assigned team ask for resources to evaluate proof of concept

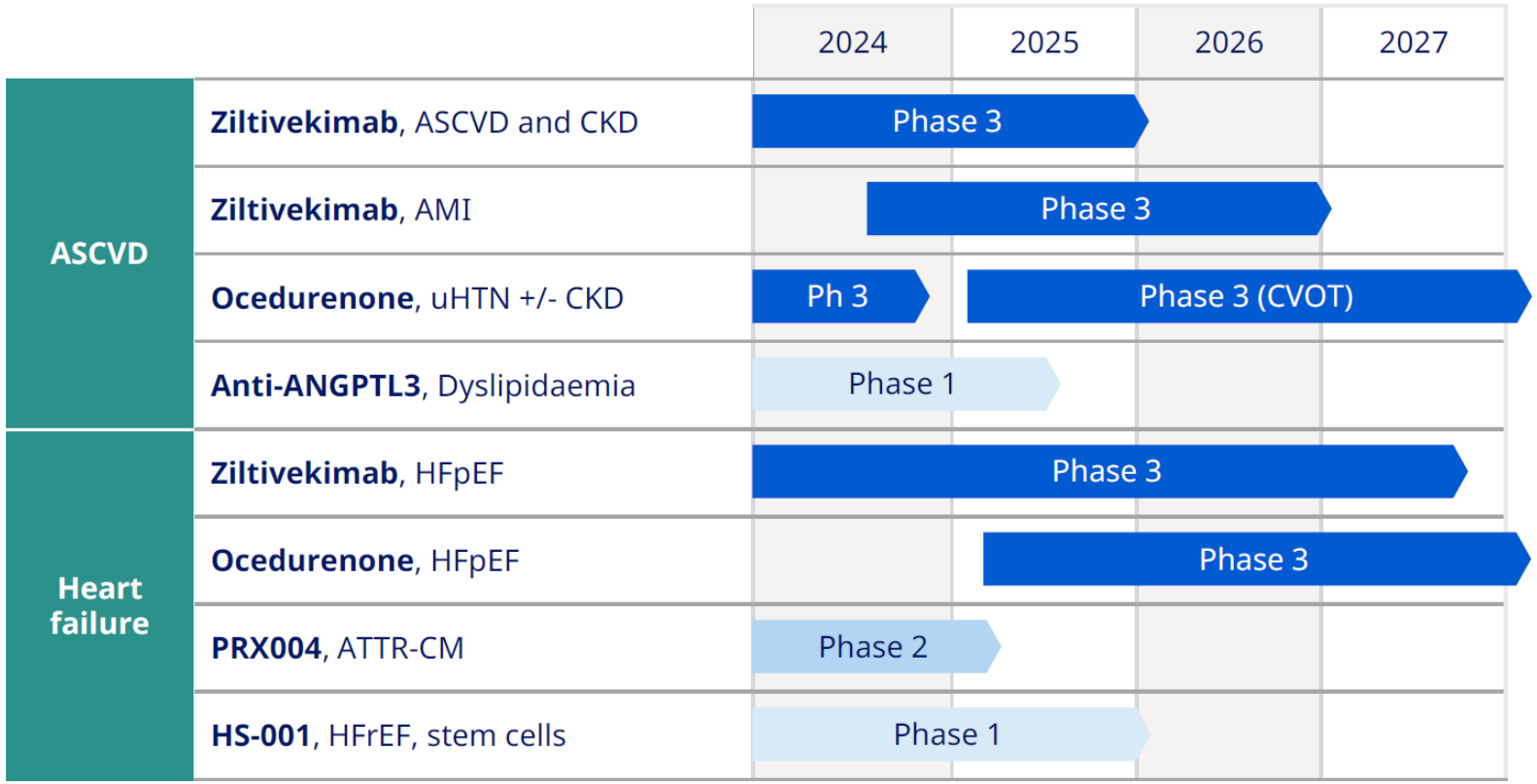
Cardiovascular disease clinical pipeline has expanded, leveraging internal and external innovation and synergies

Establishing a presence in CVD

Our key focus areas:

- Address significant unmet needs
- Pursue innovative mechanisms of action
- Combine internal and external innovation

Development pipeline



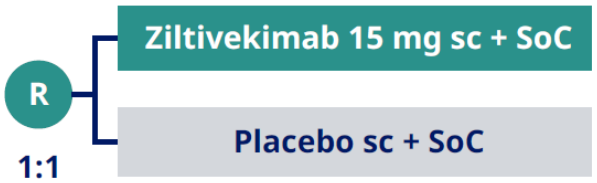
AMI: Acute myocardial infarction; ASCVD: Atherosclerotic cardiovascular disease; ATTR-CM: Transthyretin Amyloid Cardiomyopathy; CKD: Chronic kidney disease; CVD: Cardiovascular disease; HFpEF: Heart failure with preserved ejection fraction; HFrEF: Heart failure with reduced ejection fraction; uHTN: Uncontrolled Hypertension

Ziltivekimab phase 3 development programme targets high unmet need populations within CVD

ZEUS
ziltivekimab cardiovascular outcomes trial

Atherosclerosis and chronic kidney disease

n = 6,200



2021 – ~2026

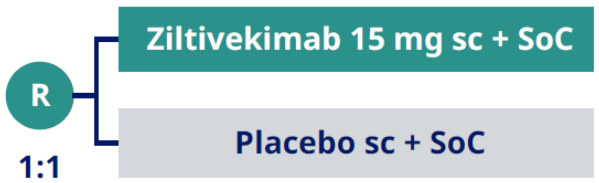
Event driven
~ 3.5 years

Primary Endpoint:
Time to the first occurrence of 3-point MACE
- Cardiovascular death
- Non-fatal myocardial infarction
- Non-fatal stroke

HERMES
ziltivekimab

HFmrEF and HFpEF

n = 5,600



2023 – ~2027

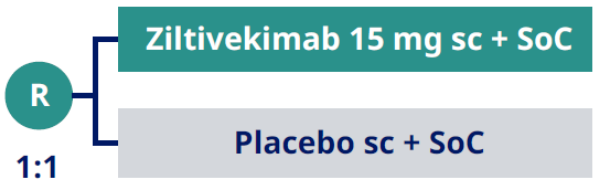
Event driven
~ 4 years

Primary Endpoint:
Time to the first occurrence of
- Cardiovascular death
- Hospitalisation for heart failure
- Urgent heart failure visit

ARTEMIS
ziltivekimab in patients with acute myocardial infarction

Acute myocardial infarction

n = 10,000



2024 – ~2027

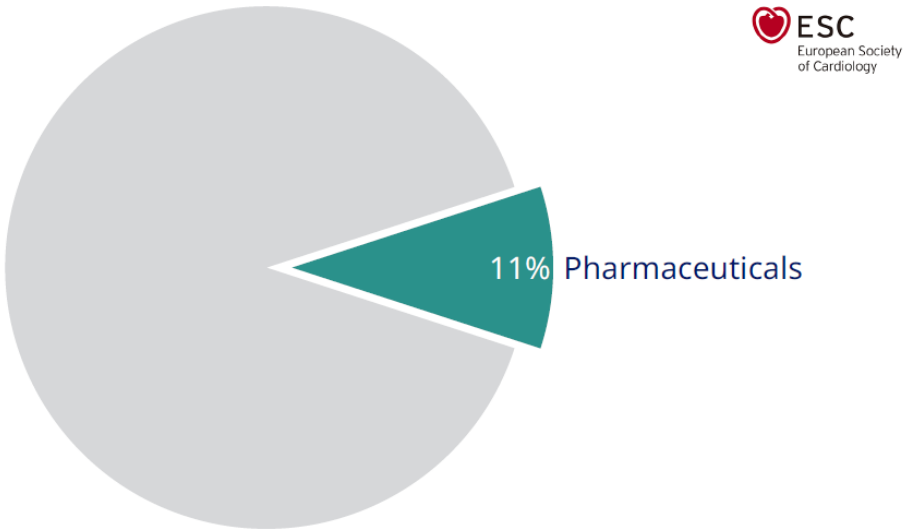
Event driven
~ 2.5 years

Primary Endpoint:
Time to the first occurrence of 3-point MACE
- Cardiovascular death
- Non-fatal myocardial infarction
- Non-fatal stroke

CVD: Cardiovascular disease; HF: Heart failure; MACE: Major adverse cardiovascular event; sc: Subcutaneous; SoC: Standard of care; HFmrEF: Heart failure with mildly reduced ejection fraction; HFpEF: Heart failure with preserved ejection fraction

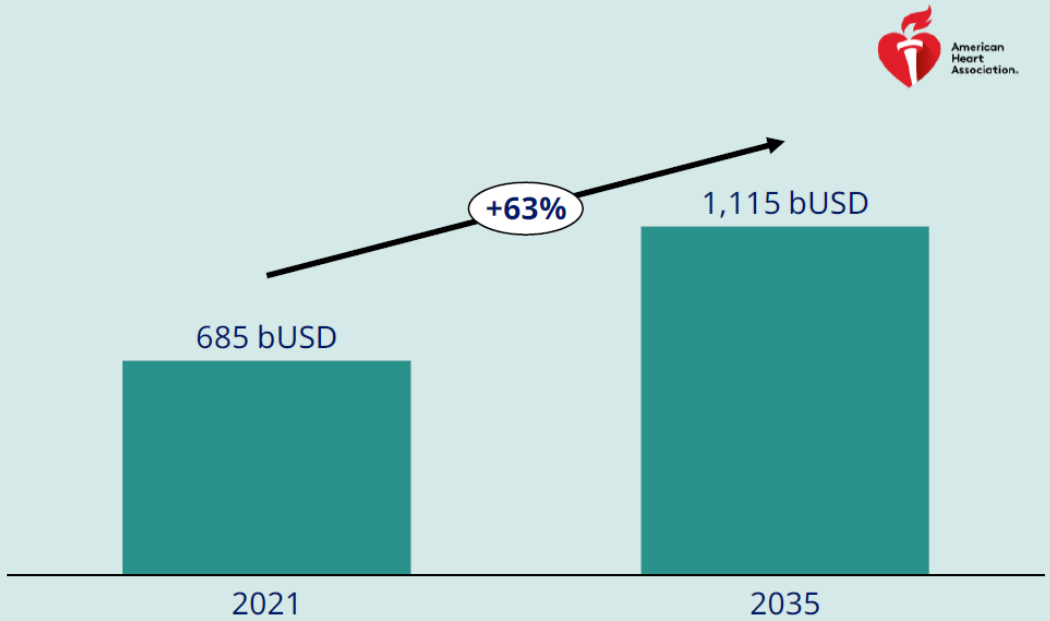
The cardiovascular market is well established with significant and growing healthcare burden

The EU annual economic burden of CVD was estimated to 282 billion EUR in 2021[1]



- Despite current treatments, 11% of EU spend from healthcare and social care budgets is on CVD
- Innovative treatments are needed to improve outcomes and limit the expected increase in CVD economic burden

The US annual economic burden of CVD is estimated to exceed 1 trillion USD in the 2030's[2]



[1]Economic burden of cardiovascular diseases in the European Union: a population-based cost study, European Heart Journal, 2023; [2]Cardiovascular disease: A costly burden for America – Projections through 2035 American Heart Association, 2016
AHA: American Heart Association; CVD: Cardiovascular disease; ESC: European Society of Cardiology; EU: European Union; US: United States

Novo Valuation Surpasses Tesla on Experimental Obesity Data

Jacob Gronholt-pedersen and Maggie Fick, *Reuters*, March 7, 2024 (excerpt)

Novo Nordisk opens new tab on Thursday surpassed Tesla Inc, opens new tab in market valuation after the maker of the popular weight-loss drug Wegovy announced positive early trial data for a highly anticipated new obesity drug.

Shares surged more than 8% to record highs, shooting Novo Nordisk up in global rankings to the 12th most valuable company from 14 previously, after it told investors a Phase I trial of the pill version of experimental drug amycretin showed participants lost 13.1% of their weight after 12 weeks.

That compares to a weight loss of about 6% after 12 weeks and 15% after 68 weeks in trials for Wegovy, its blockbuster obesity drug. Investors welcomed the news as indicating Novo had more in its pipeline beyond its hugely successful Wegovy. Its shares have soared since launching the weekly injections in the United States in 2021. Novo's shares have risen more than three-fold since June 2021 when it launched Wegovy in the United States, last year becoming Europe's most valuable listed company, ahead of LVMH.

On Thursday, its market valuation reached $566 billion, ahead of Tesla and Visa, opens new tab, according to LSEG data.
"Novo has made clear that the amycretin molecule likely will form the foundation of the company's rapidly growing pipeline," said Guggenheim analyst Seamus Fernandez.

Nearly half of Novo's current valuation is based on the company's pipeline of new experimental drugs such as amycretin, according to calculations by Berenberg analysts last week.

Source: https://www.reuters.com/business/healthcare-pharmaceuticals/novo-nordisk-present-early-stage-trial-data-new-diabetes-drug-investor-meeting-2024-03-07/

Novo Nordisk is continuing the development of a portfolio of superior treatment solutions for obesity

Building a leading portfolio

Our key focus areas

- Double-digit weight loss
- Composition of weight loss
- Co-morbidity impact
- Safety and tolerability
- Dosing frequency

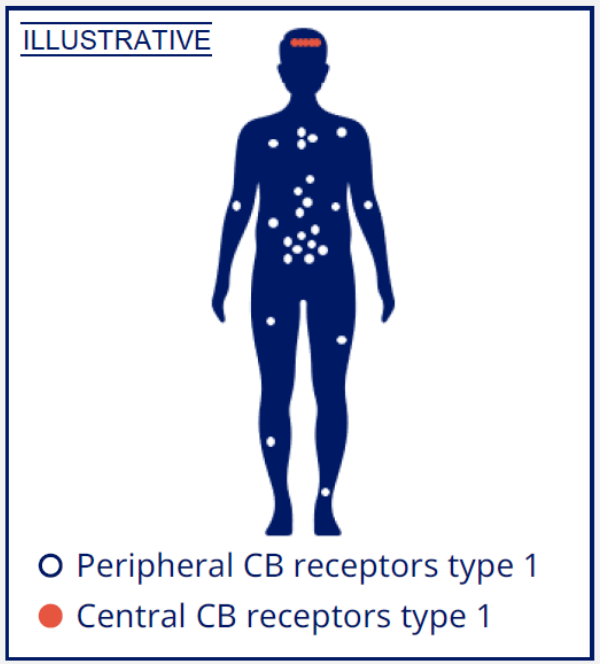
Development pipeline

		2024	2025	2026	2027
Obesity	**SELECT**, sema 2.4 mg, CVOT	Regulatory decision in US and EU			
	STEP HFpEF[1], sema 2.4 mg	Regulatory decision in US and EU			
	Oral semaglutide, 25 and 50 mg	Ph 3			
	Semaglutide 7.2 mg	Phase 3			
	CagriSema	Phase 3			
	Monlunabant (INV-202) Oral CB1R inverse agonist	Phase 2			
	OW GIP/GLP-1	Phase 2			
	GELA[2] Peripheral focused ultrasound	Phase 2			
	INV-347 Oral CB1R inverse agonist	Phase 1			
	Amycretin OW sc and OD oral co-agonist[3]	Phase 1			

[1] Includes both the STEP HFpEF obesity trial and the type 2 diabetes trial; [2] In collaboration with GE Healthcare; [3] Note this trial was completed in Q4 2023. Hence, the ongoing phase 1 trial is OW sc amycretin
EU: European Union, US: United States
CB1R: Cannabinoid receptor 1; CVOT: Cardiovascular outcome trial; GIP: Gastric inhibitory polypeptide; OD: Once-daily; OW: Once-weekly; Ph: Phase; Sc: Subcutaneous; Sema: Semaglutide; Ph: Phase

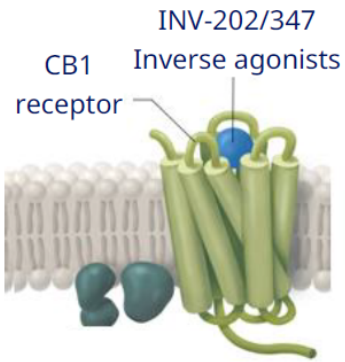
CB1R inverse agonism holds potential as a novel mechanism of action both as monotherapy and add-on treatment

CB1R are found throughout the body



- CB1 biology plays a role in regulation of energy homeostasis[1]

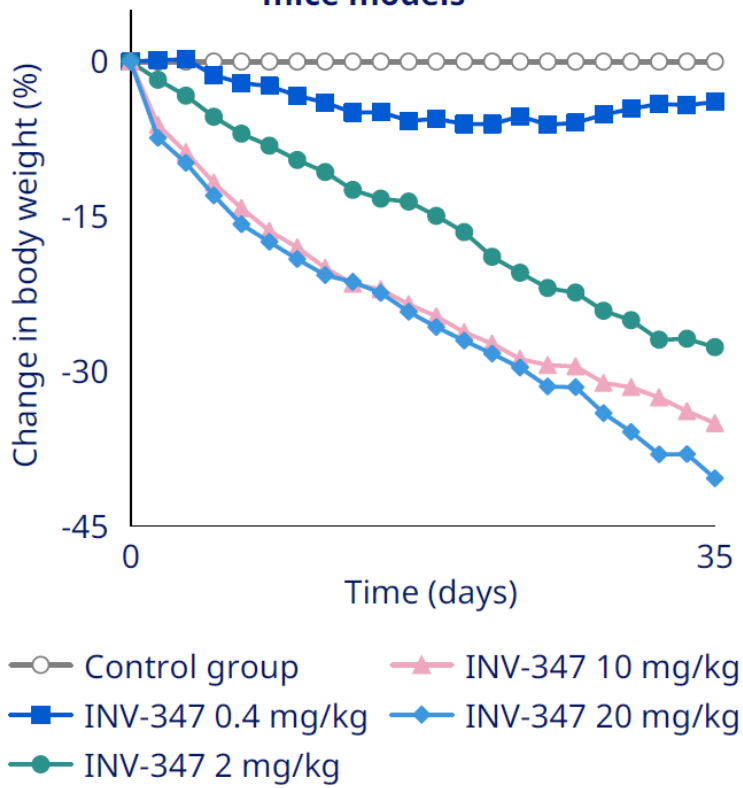
Inversago next-generation CB1R molecules



- Novel design minimising brain penetration

Monlunabant (INV-202) appeared to have a **safe and well-tolerated profile** with no serious or severe treatment-emergent adverse events in a phase 1 trial

INV-347 shows weight loss in DIO mice models

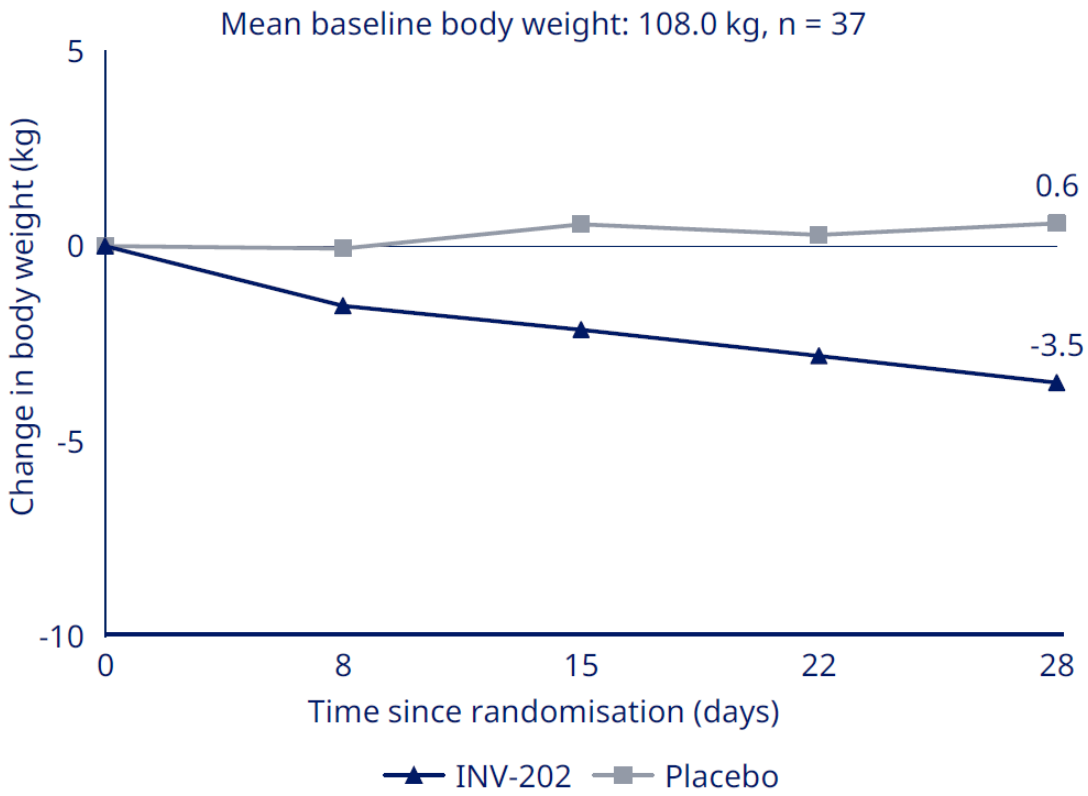


[1]Dörnyei G, et al. Biomedicines. 2023 Jan 21;11(2):306. doi: 10.3390/biomedicines11020306
CB: Cannabinoid; CB1R: Cannabinoid receptor type 1; DIO: Diet induced obesity

CMD24 CAPITAL MARKETS DAY

Monlunabant (INV-202) is an oral small molecule CB1R inverse agonist showing weight loss potential in phase 1

INV-202 showed mean weight reduction of -3.5kg at day 28



Highlights of the monlunabant (INV-202) trial

Phase 1 Results

- Monlunabant appeared to have a safe and well-tolerated profile. The most common side effects were gastrointestinal
- Monlunabant produced a statistically significant mean weight loss of 3.5 kg (3.3%) compared to 0.6 kg (0.5%) with placebo at day 28

Next steps:

- Phase 1 initiated with the next-generation molecule INV-347
- Phase 2 studies ongoing in Diabetic kidney disease and Obesity

CB1R: Cannabinoid receptor 1; OD: Once-daily
Note: The data shown is based on a post-hoc analysis of the phase 1b study of INV-202

Amylin shows potential for additional and complementary benefits to GLP-1 in metabolic diseases

Amylin and GLP-1 are endocrine peptide hormones

Amylin	GLP-1
	
β-cells in pancreas	L-cells in intestines

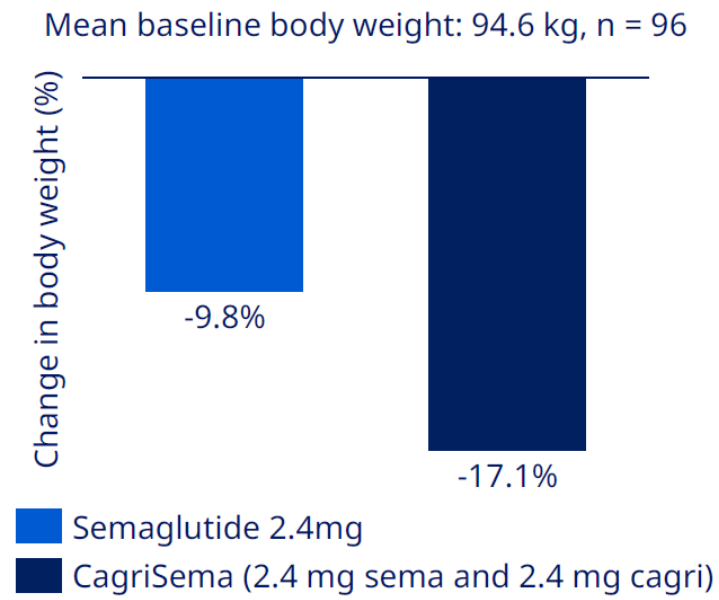
Amylin and GLP-1 both have a role in[1,2]:

- Appetite regulation (hunger and satiety)
- Glucose control

Amylin is also involved in[2,3]:

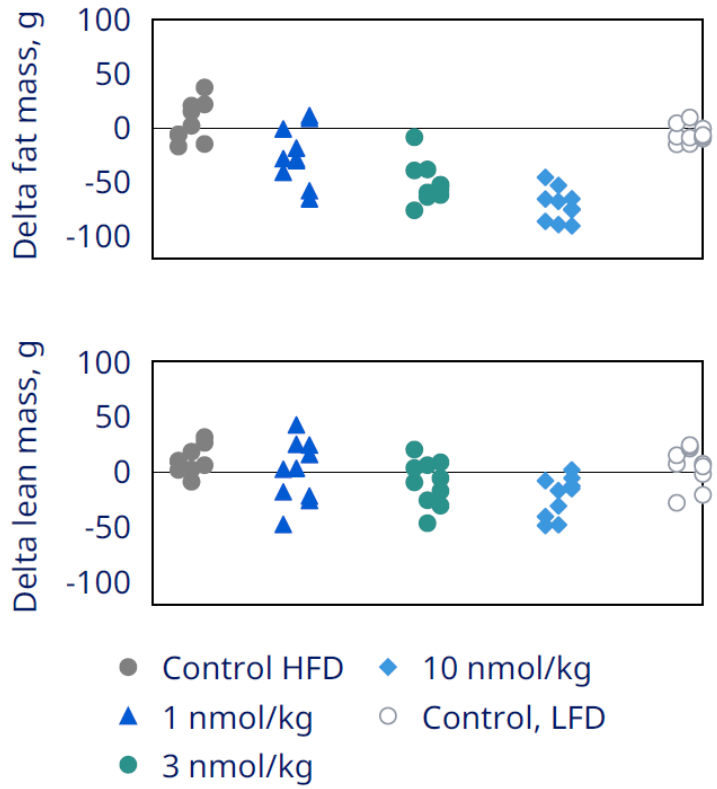
- Bone homeostasis
- Body composition

Weight loss in a 20-week phase 1 obesity trial



Novo Nordisk amylin analogues have appeared to have **safe and well-tolerated profiles** in clinical trials

Cagrilintide improves body composition in obesity DIO rat model[3]

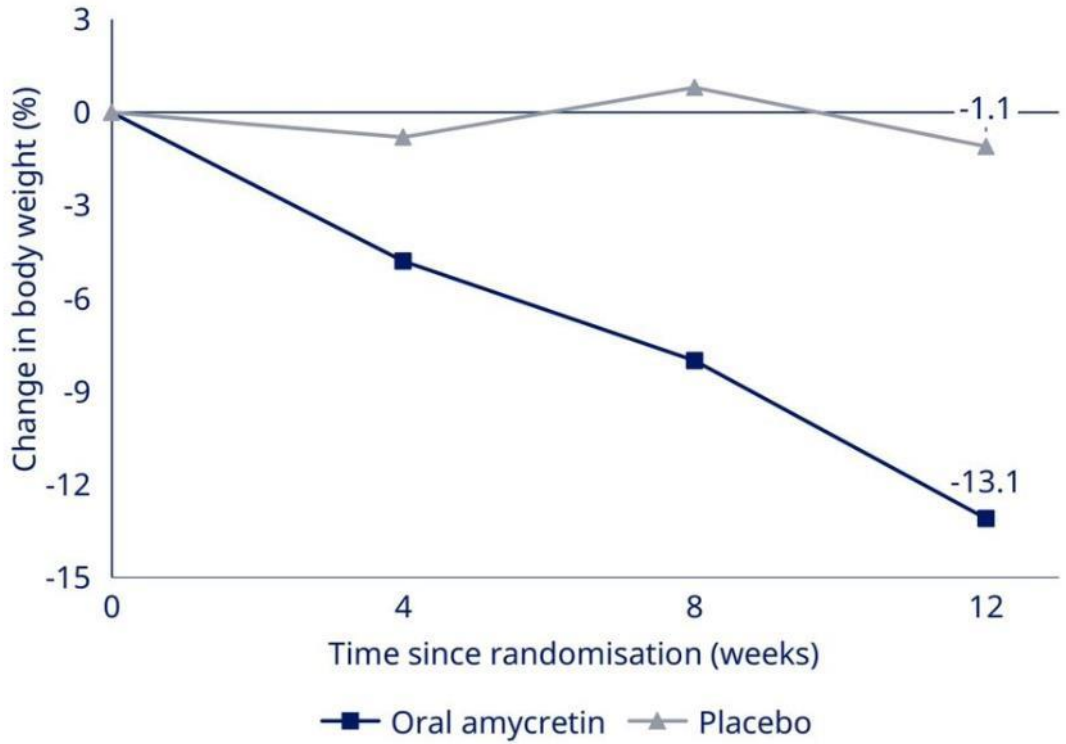


[1]Campbell et.al. Cell Metabolism 2013 (17) 819-837; [2]Hay et al. Pharmacological reviews 2015 (67) 564-600; [3]Daquin et.al. 2004 164(4):509-14
Cagri: Cagrilintide; DIO: Diet induced obesity; g: gram; HFD: High-fat diet; LFD: Low-fat diet; nmol: nanomole; Sema: semaglutide

Oral amycretin phase 1 trial completed and subcutaneous amycretin phase 1 trial ongoing with expected read-out in 2025

Results from oral amycretin phase 1 on weight loss

Mean baseline body weight: ~89 kg, n = 16



Amycretin development programme in obesity

Phase 1:

- ✓ Oral amycretin phase 1 completed
- Subcutaneous amycretin phase 1 ongoing

Next steps:

- Subcutaneous amycretin phase 1 expected completion in 2025
- Clinical development programme to be defined based on subcutaneous amycretin phase 1 data

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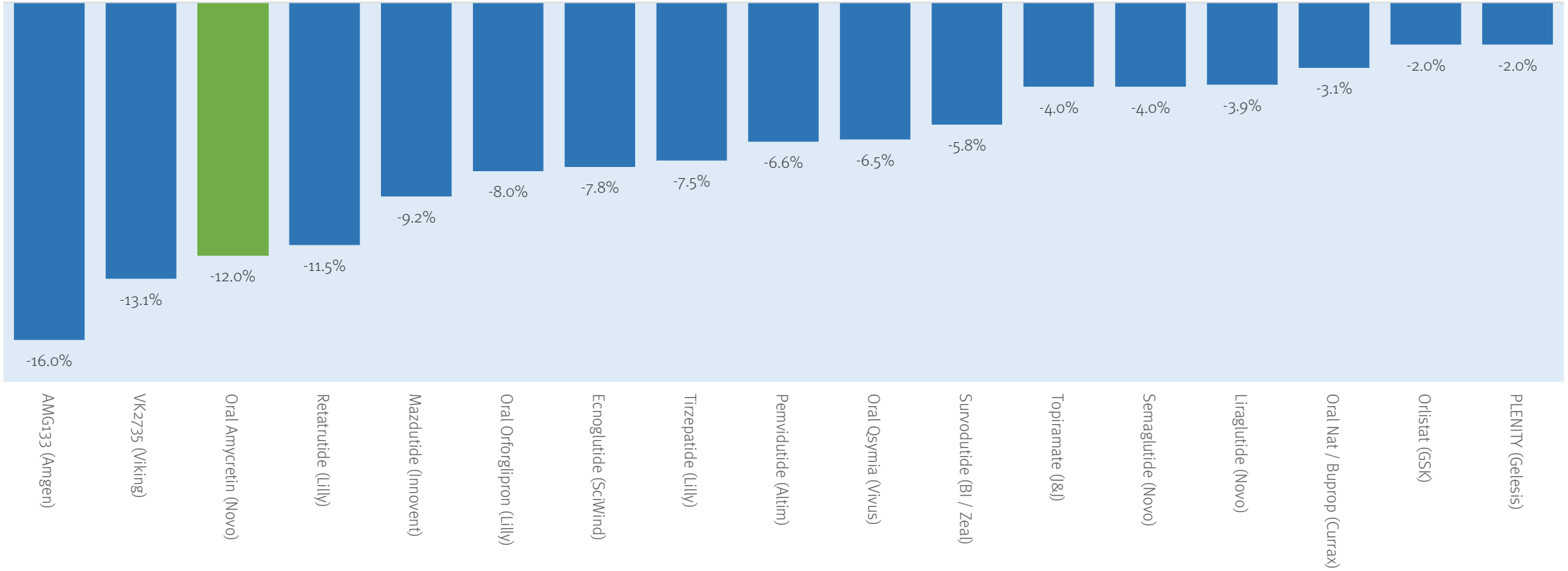
Amycretin Weight Loss Best Seen for an Oral at 12 Weeks

While Novo's results disclosed in its investor day are highly impressive, the company has not yet disclosed side effect and tolerability data for patients treated in the trial that lost weight.

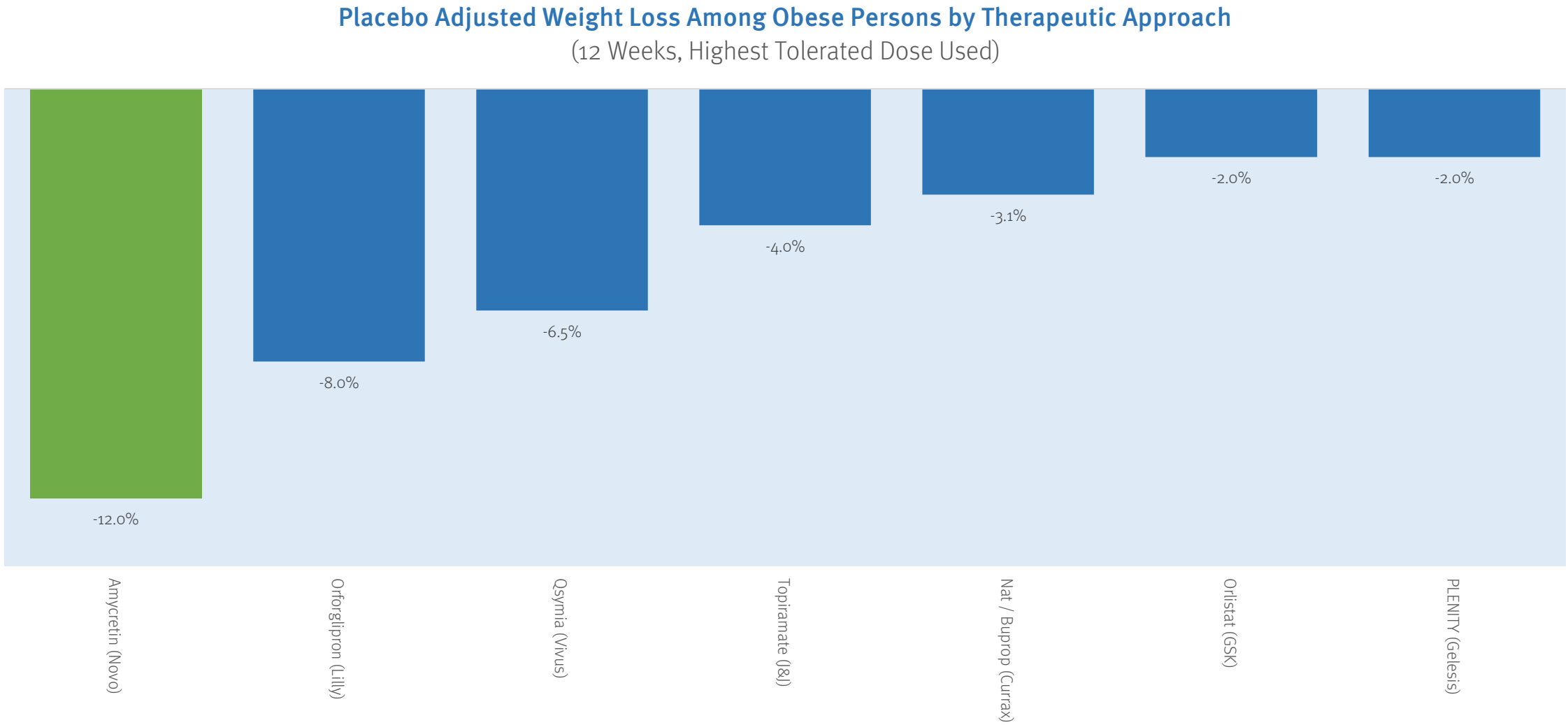
Placebo Adjusted Weight Loss Among Obese Persons by Therapeutic Approach

(12 Weeks, Highest Tolerated Dose Used)



Source: Stifel analysis of weight loss trials. Note that trials did not involve direct comparisons of the agents and may have participants with different baseline characteristics who were treated differently by trial.

Weight Loss Seen With Oral Drug Candidates at 12 Weeks



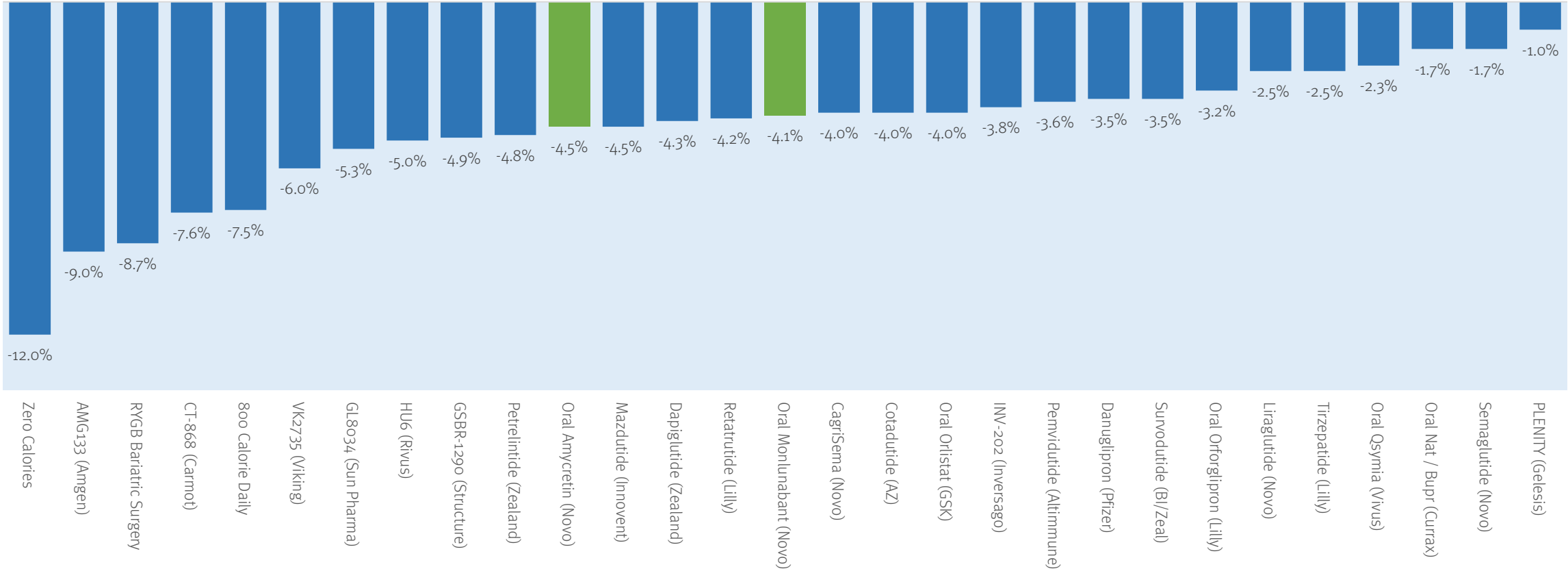
Source: Stifel analysis of weight loss trials. Note that trials did not involve direct comparisons of the agents and may have participants with different baseline characteristics who were treated differently by trial.

Amycretin Weight Loss Not Best Seen for an Oral at 4 Weeks

The landscape for oral weight loss agents is far more competitive at four weeks. It's also important to note that Novo's CB1 antagonist, Monlunabant delivered excellent weight loss at four weeks.

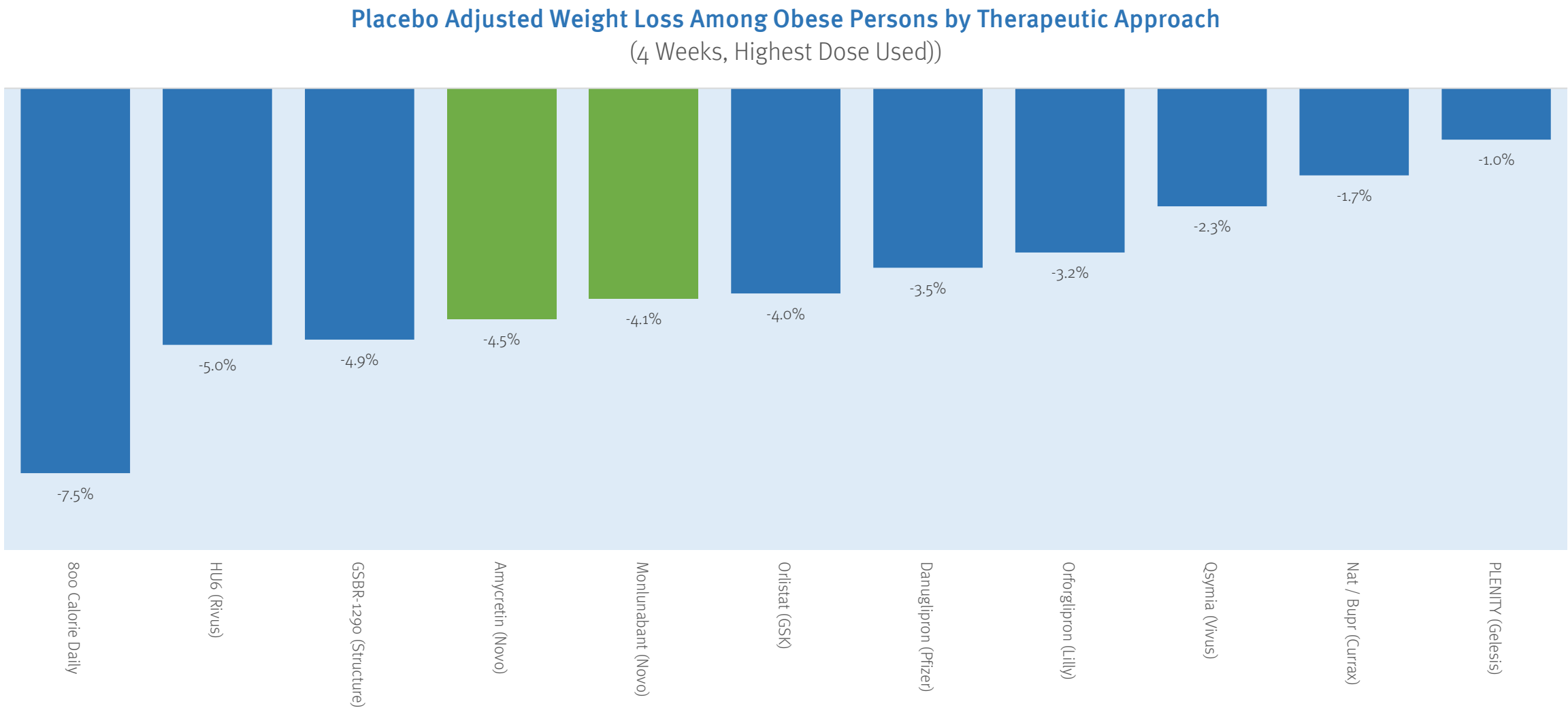
Placebo Adjusted Weight Loss Among Obese Persons by Therapeutic Approach

(4 Weeks, Highest Dose Used))



Source: Stifel analysis of weight loss trials. Note that trials did not involve direct comparisons of the agents and may have participants with different baseline characteristics who were treated differently by trial.

Weight Loss Seen With Oral Drug Candidates at 4 Weeks



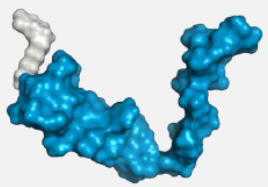
Source: Stifel analysis of weight loss trials. Note that trials did not involve direct comparisons of the agents and may have participants with different baseline characteristics who were treated differently by trial.

New standalone and tri-agonist molecule to enter phase 1 within the next 12 months, with new concepts to follow

Expected phase 1 initiations within the next 12 months

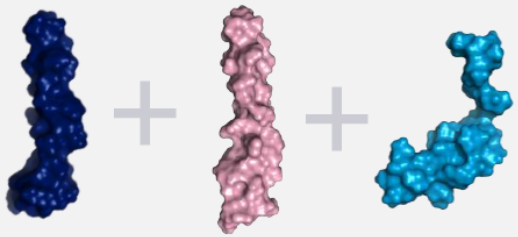
New amylin

- Phase 1 initiation expected in 2024
- New molecule for mono-therapy provides opportunity for weight management
- Potential for combination therapy



New tri-agonist

- Phase 1 initiation expected within next 12 months
- Potential for improved weight loss efficacy
- Potential for improved effect on obesity related comorbidities



ILLUSTRATIVE

Focus areas for upcoming projects

- Regulating appetite and energy expenditure
- Weight maintenance
- Lean body mass preservation
- Sustained release

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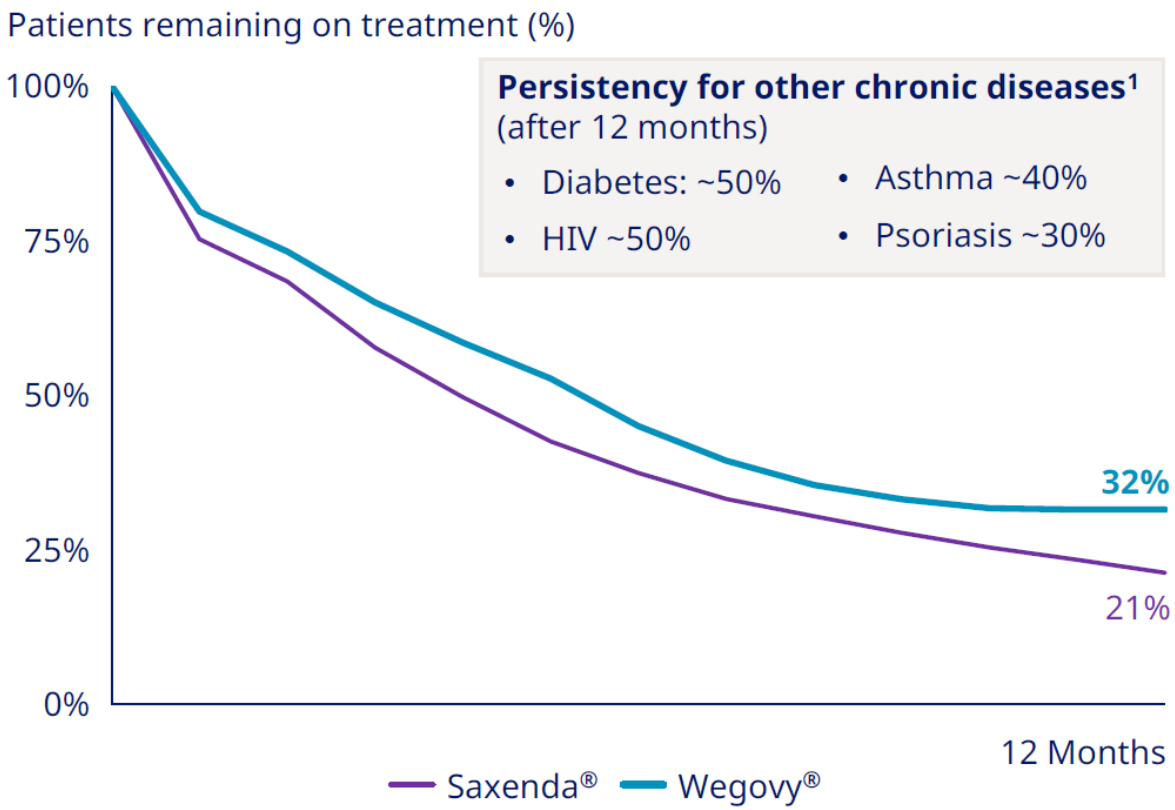
Novo Nordisk is broadening focus from solely weight loss to improving health for patients with overweight or obesity

Patient persistency on anti-obesity medications after 12 months



Persistency for other chronic diseases[1]
(after 12 months)

- Diabetes: ~50%
- HIV ~50%
- Asthma ~40%
- Psoriasis ~30%

Characteristics for patients on Wegovy® in the US

≈ 75% naïve to AOM treatment

- 81% female
- Age: Average of 47 years
- Average BMI of 38
- Patients on Wegovy® with type 2 diabetes diagnosis: 8%
- With comorbidities:
  ≥1: 78% ≥2: 53% ≥3: 32%
- Average Wegovy® stay time >6 months despite supply constraints[2]

[1]Hichborn, et al. (2018). Improving patient adherence through data-driven insights. McKinsey & Company; [2] Based on real world data, patient cohort included those initiating therapy between Oct '21 and Mar '22, followed for 1 year;
AOM: Anti-obesity medications; BMI: Body mass index; HbA1c: Haemoglobin A1c; HIV: Human Immunodeficiency Virus; US: United States
Source: IQVIA LAAD AOM Rx August 2023; Real world evidence based on prescription data

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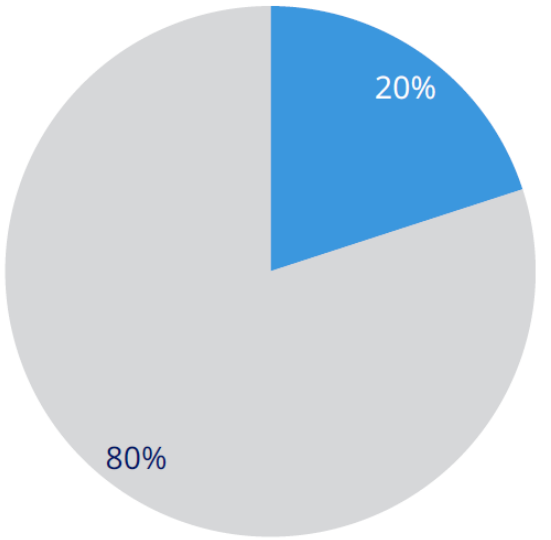
Anti-obesity medications are expected to be mostly out-of-pocket, with SELECT as key lever to improve reimbursement

Majority of IO AOM sales are currently OOP

INDICATIVE



Current AOM reimbursement examples

wegovy® semaglutide injection 2.4 mg

UK	**BMI ≥35** or BMI ≥ 30 with ORC

Saxenda® liraglutide injection

COL	**BMI ≥30** with two ORCs
CH	**BMI ≥28 with ≥1 ORC** or BMI ≥35

15 countries have selected reimbursement for Saxenda®

SELECT could improve access to Wegovy®

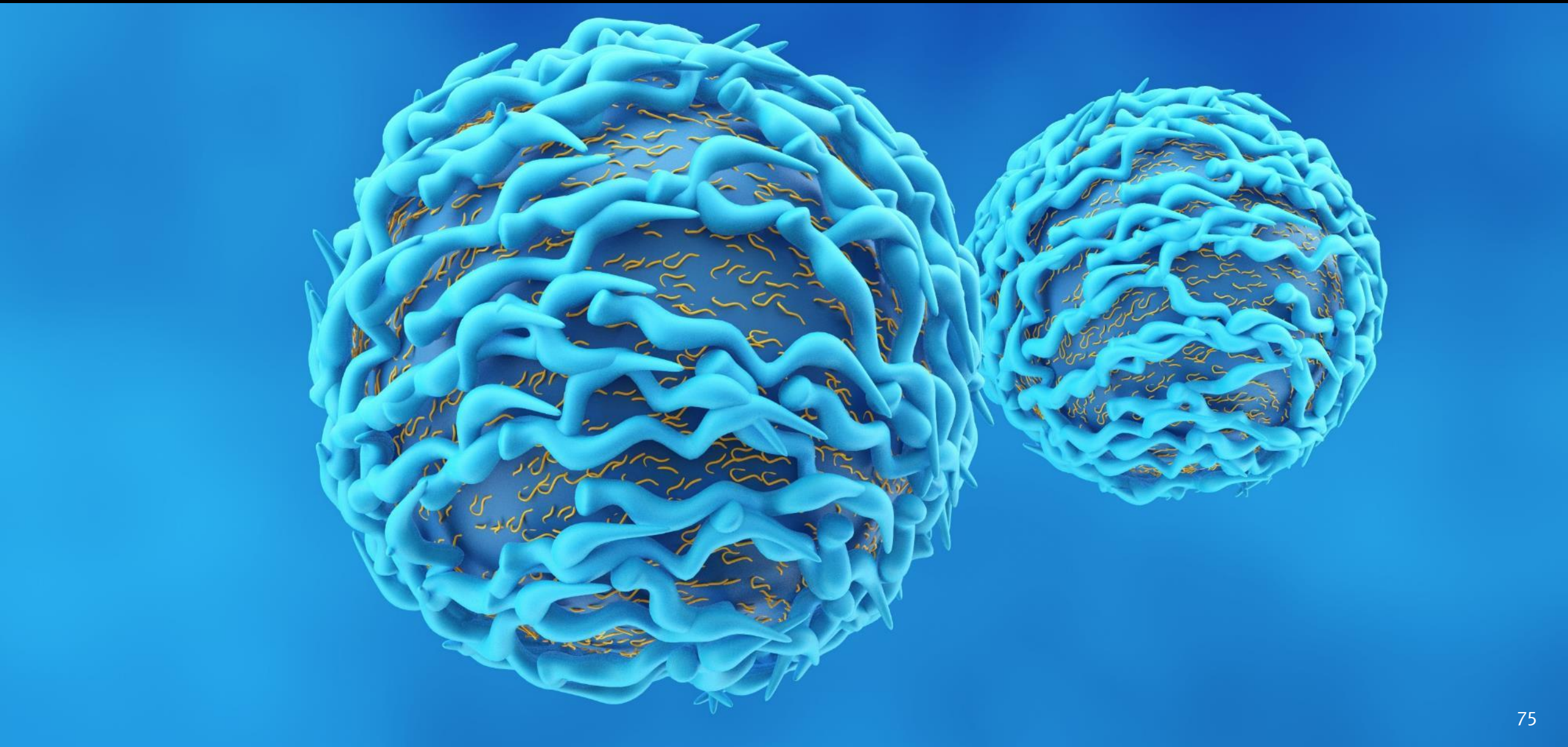
Wegovy® reimbursed
Leverage SELECT to expand or improve market access

Wegovy® not reimbursed
Use SELECT to open or re-open reimbursement negotiations

Out-of-pocket
Increase willingness to pay in out-of-pocket markets

AOM: Anti-obesity medication; BMI: Body mass index; CH: Switzerland; COL: Columbia; IO: International Operations; OOP: Out-of-pocket; ORC: Obesity-related comorbidity; UK: United Kingdom
Note: Break-down of IO AOM sales is an estimate and cover both Saxenda® and Wegovy®

Immunology Update



Rationale to Invest in Immunology Field

1

Immunology field is hitting translational inflection points in key areas

- Kinase inhibitors (e.g., JAK inhibitors) giving patients oral options
- Minibodies and extended life drugs game-changing for patients
- FcRn system
- Innate Immune system

2

Huge potential of drugs

- High efficacy
- Improving side effect profile
- Good reimbursement
- Most drugs have multiple indications (“pipeline in a drug” phenomenon)

3

Financial Upside

- Revenues expected to exceed $100 billion by 2024
- Long-term double digit growth rate in immunology
- Significant M&A volume in the field

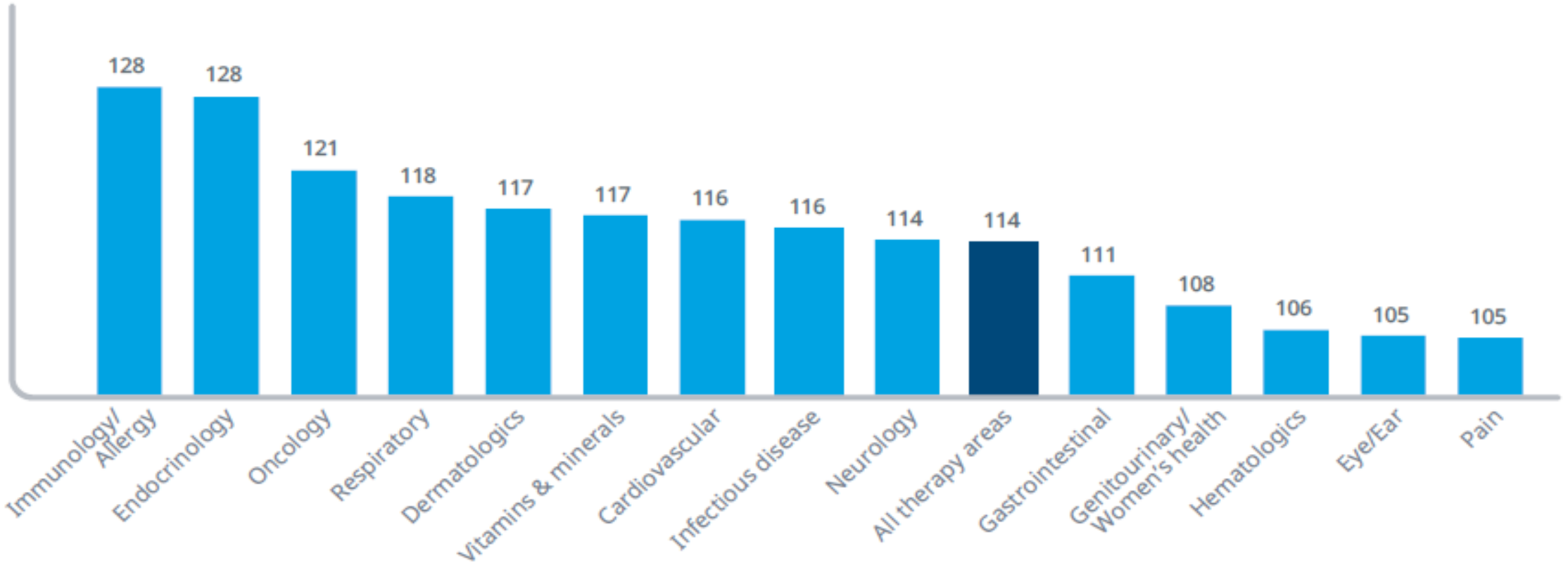
4

Precision Opportunity

- Possible to stratify patients by cytokine levels at baseline.
- Emerging technologies for immuno-surveillance permit patient enrichment and segmentation strategies

Immunology Has Been the Fastest Growing Area of Medicine Since 2018

Exhibit 6: Defined daily doses (DDD) in 2023 across select therapy areas indexed to 2018 values (2018 value = 100)

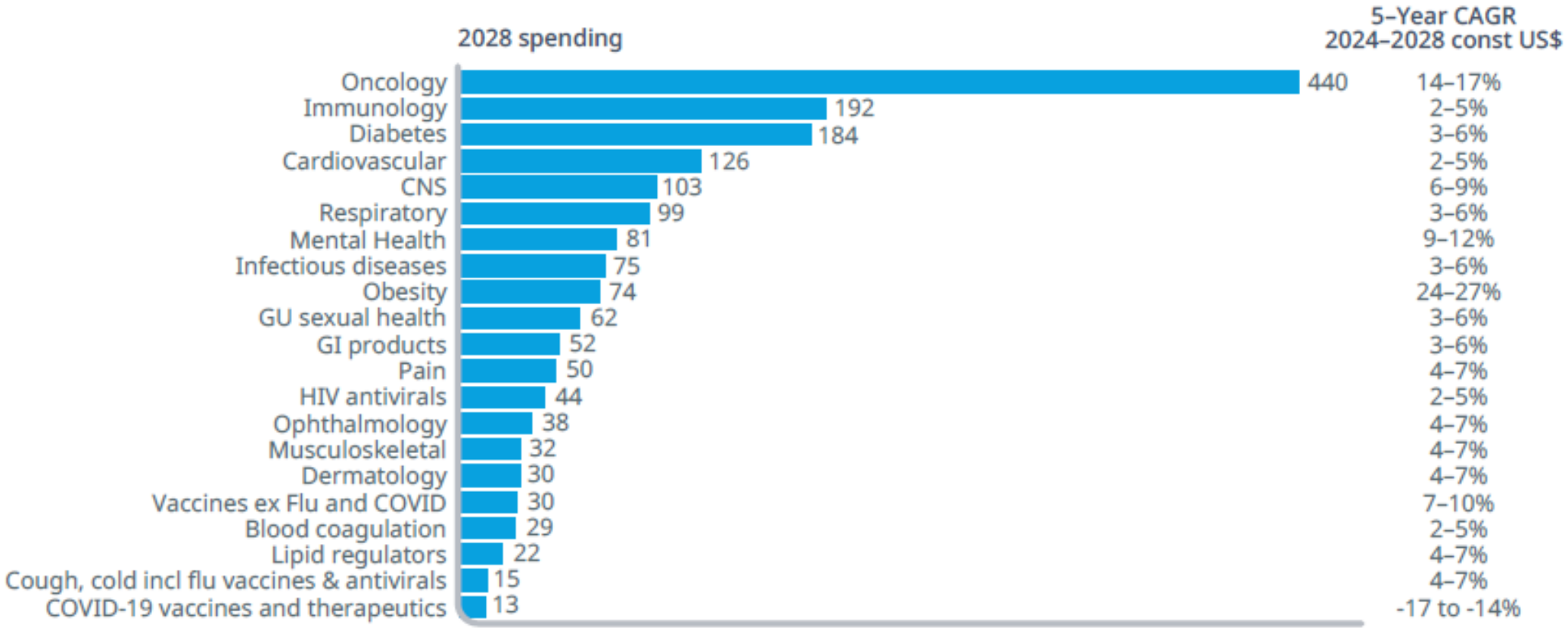


Source: IQVIA MIDAS, Jun 2022; IQVIA Institute, Dec 2023.

Source: IQVIA Institute, Global Use of Medicines Report, January 2024

Immunology Forecast by IQVIA Institute to be the Second Largest Area of Pharma Spend (After Oncology) in 2028

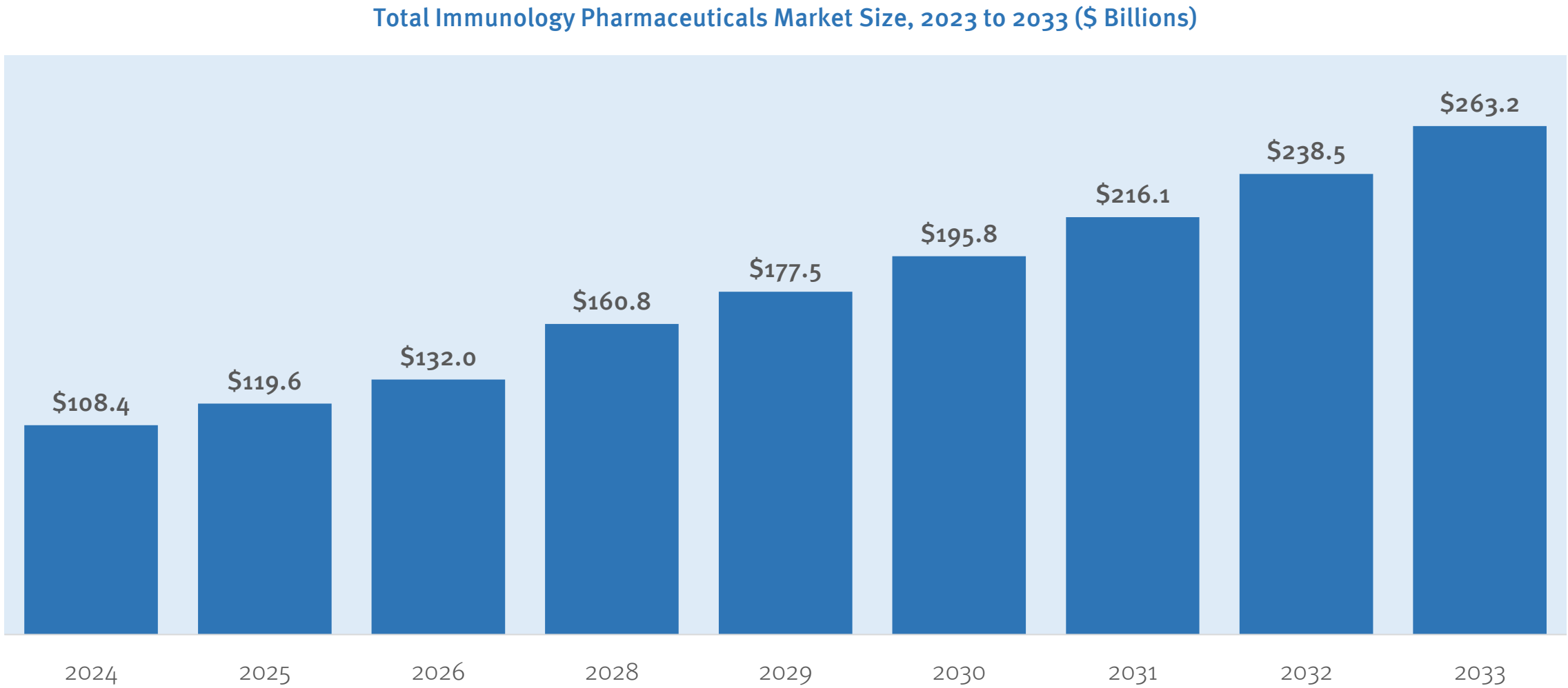
Exhibit 37: Top 20 therapy areas in 2028 in terms of global spending with forecast 5-year CAGRs, const US$Bn



Source: IQVIA Forecast Link, IQVIA Institute, Dec 2023.

Source: IQVIA Institute, Global Use of Medicines Report, January 2024

Immunology Market Size to Increase More than $150 Billion Between Now and 2033



Source: Precedence Research (https://www.precedenceresearch.com/immunology-market)

Explosion of Industry Interest in ImmunoScience

The market for immunologically-linked drugs is just getting started and is likely to become much larger than it is today.

Growing Interest in this Field:

To date, we have seen certain drugs aimed at autoimmune disease and certain other inflammatory conditions take a substantial share of the patient dollar for pharmaceutical expenditures.

Some of the largest drugs on the market today (e.g., Skyrizi®, Enbrel®) are for the treatment of autoimmune diseases such as Crohn's Disease, Psoriasis and Rheumatoid Arthritis. These drugs have focused on controlling inflammatory cytokines, largely through the T-cell system.

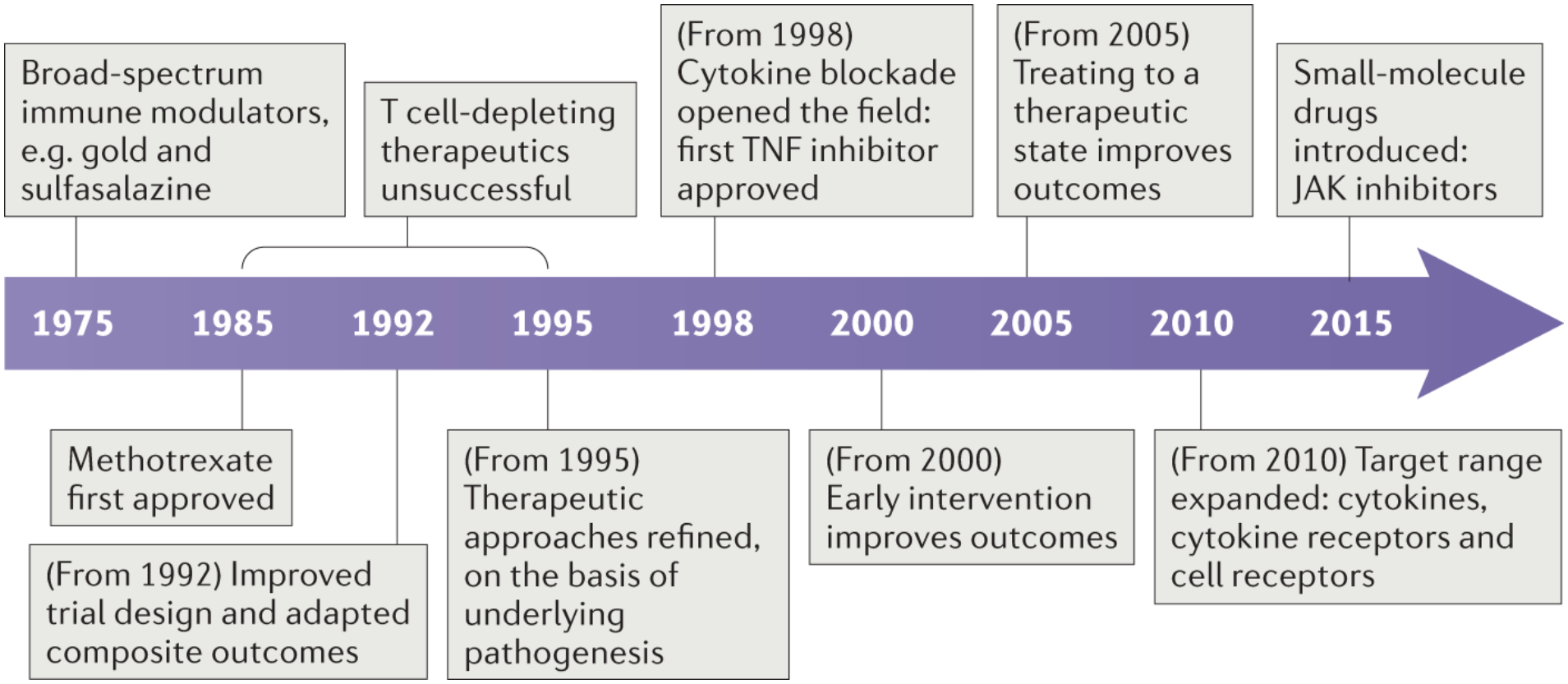
There is an emerging perspective by some in the therapeutics sector that the potential for inflammatory drugs and autoimmune drugs is far broader. In particular, there is huge untapped potential for pharmacology in the B-Cell system, the complement system, the FcRn system and the innate immune system.

Some might argue that more than half of human disease is associated with inflammatory / immunological conditions (including neurology, heart disease, some cancer, liver disease and gout).

Further, recent developments in the complement area, with CAR-t and the understanding of the role of the Fc neonatal receptor have led to the view that there may be more than fifty diseases (some of which are rare) that could be addressed by new classes of drugs targeted at autoantibodies.

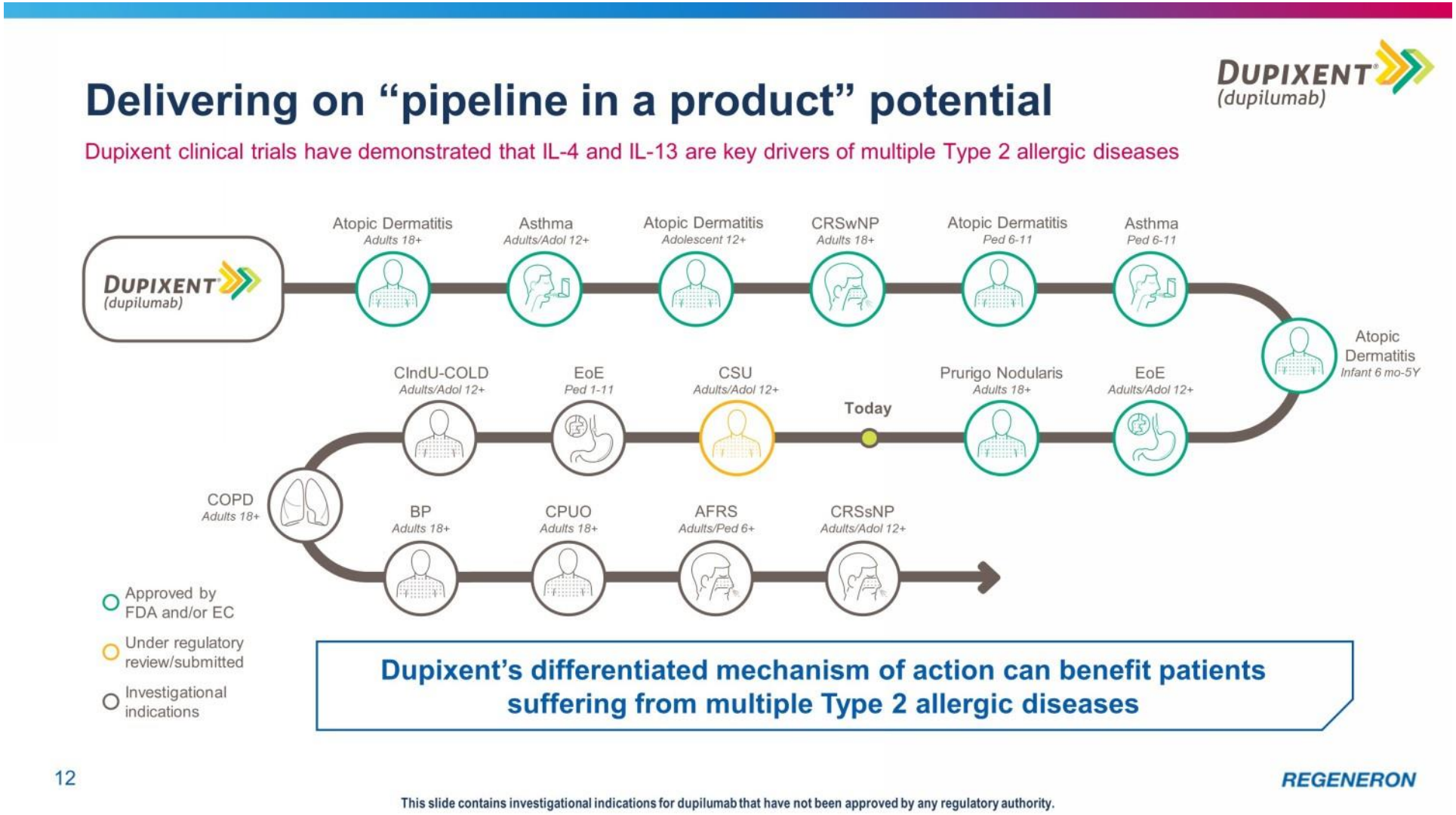
Today's Immunology Pharmaceuticals Emerged from Five Decades of Research Focused on Increasing Results While Moving Away from Broad Spectrum Immunomodulators.

This timeline highlights the key lessons learnt over the past 40 years that led to the development of immune therapeutics, from broad spectrum to highly specific, for immune-mediated inflammatory diseases. JAK, Janus kinase; TNF, tumour necrosis factor:



Source: McInnes, I.B., Gravallese, E.M. Immune-mediated inflammatory disease therapeutics: past, present and future. *Nat Rev Immunol* **21**, 680–686 (2021).

Often Possible to Get Many Indications on the Label of Immunology Drugs ("Pipeline in a Product" Concept)



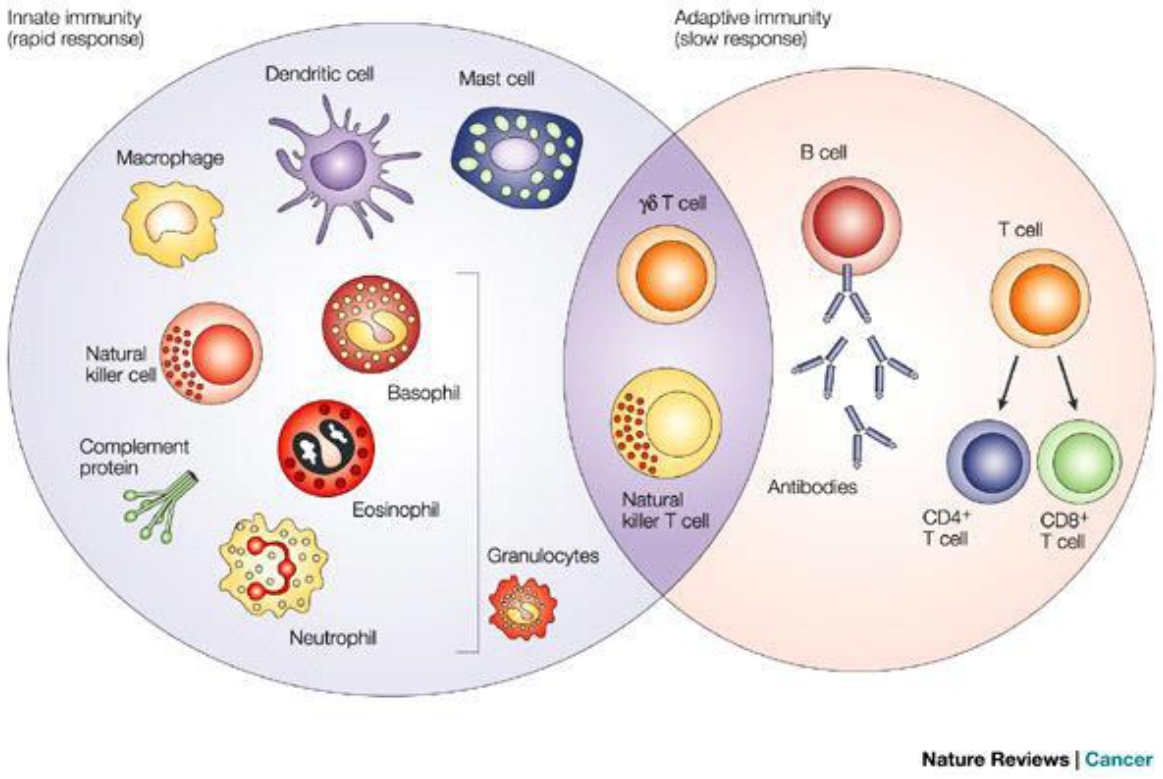
Immunology Basics

The immune system is comprised of a network of cells, tissues, and organs that interact to protect the body against viruses, bacteria, and other pathogens. The innate immune system is the first line of attack against foreign invaders and functions through mononuclear cells such as macrophages which can engulf a foreign object, NK cells, eosinophils and neutrophils.

The innate and adaptive system communicate with each other via NK cells, dendritic cells and T-cells.

The innate system is rapid but not specific to an antigen while the adaptive system is antigen-specific (and thus more likely to be effective) but slower.

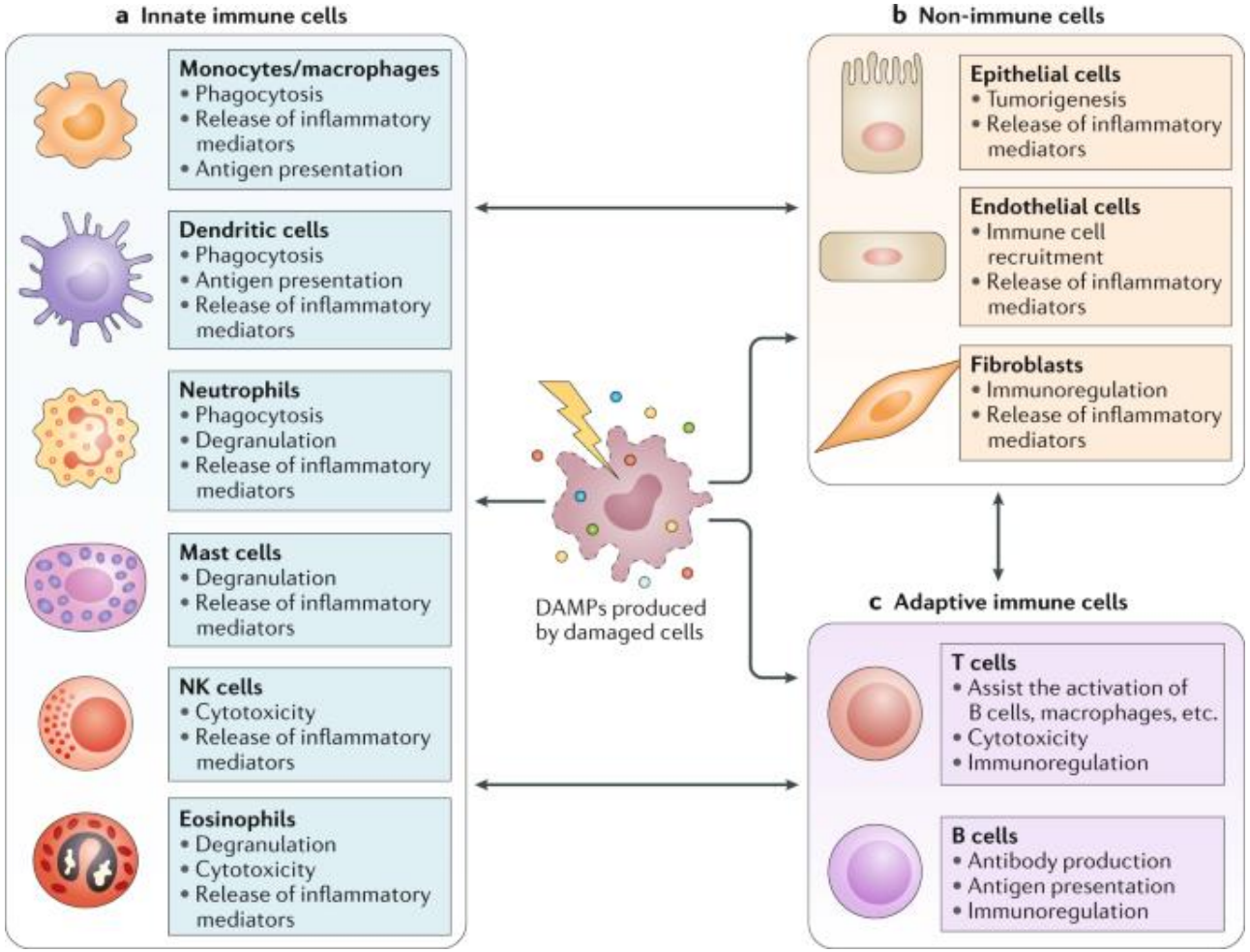
The adaptive immune system develops a customized response to the specific investor. When a foreign antigen enters the body the first step is the signaling of antigen-presenting cells (APCs), which include B lymphocytes (B cells) to T lymphocytes (T cells). T cells can then attack and destroy the foreign organisms in several ways. The antigen-specific antibodies produced by the B cells, remain to facilitate clearance of the foreign antigen and can themselves kill an invader using ADCC.



Source: Stifel Research, *Nature Reviews Cancer*, 4, 11-22, 2004.

Adaptive and Innate Immune System Cross Talk Directly and via Non-immune Cells and DAMPs

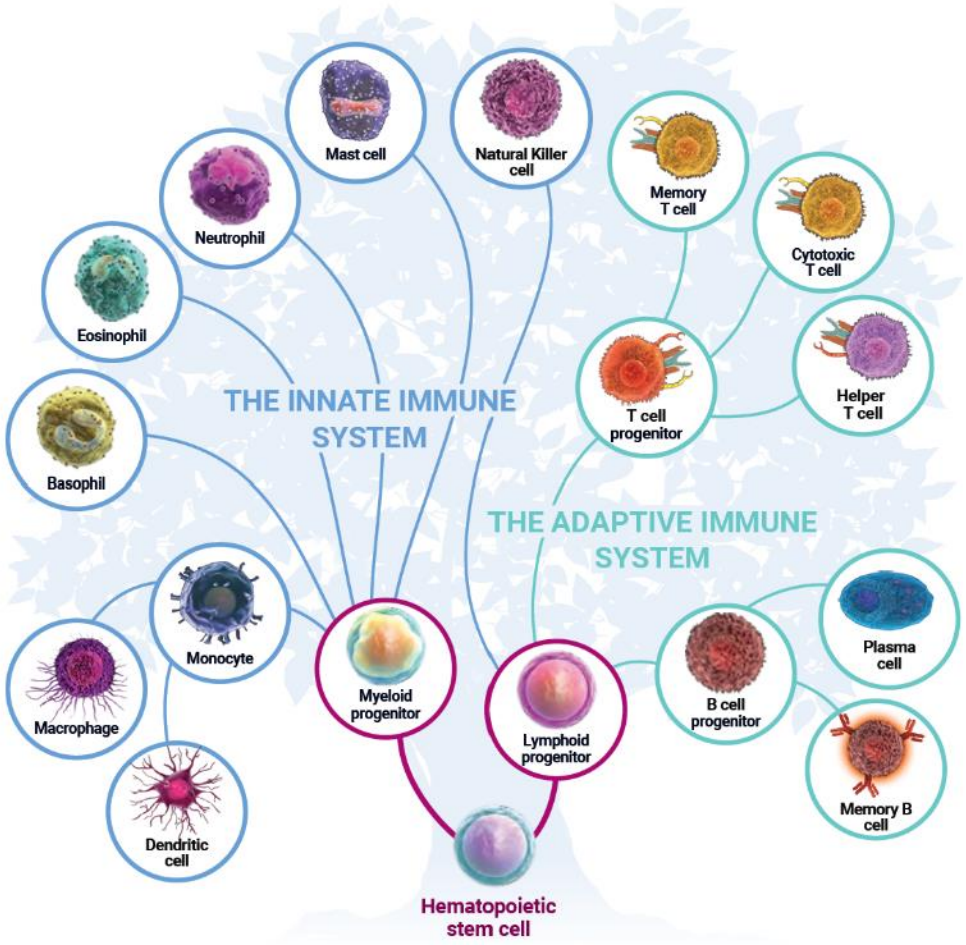
The innate immune system has the capacity to detect ‘non-self’ molecules derived from pathogens, known as pathogen-associated molecular patterns, via pattern recognition receptors. In addition, an increasing number of endogenous host-derived molecules, termed damage-associated molecular patterns (DAMPs), have been found to be sensed by various innate immune receptors. The recognition of DAMPs, which are produced or released by damaged and dying cells, promotes sterile inflammation, which is important for tissue repair and regeneration, but can also lead to the development of numerous inflammatory diseases, such as metabolic disorders, neurodegenerative diseases, autoimmune diseases and cancer. Here we examine recent discoveries concerning the roles of DAMP-sensing receptors in sterile inflammation and in diseases resulting from dysregulated sterile inflammation, and then discuss insights into the cross-regulation of these receptors and their ligands.



Source: Gong, T., Liu, L., Jiang, W. et al. DAMP-sensing receptors in sterile inflammation and inflammatory diseases. *Nat Rev Immunol* 20, 95–112 (2020).

Immune Cells Derive from Hematopoietic Stem Cells

Immune cells are differentiated via certain cytokines and in turn secrete many other cytokines (signaling molecules) when activated.



HEMATOPOIETIC STEM CELL		
	SELF-RENEWAL CYTOKINES	EXPANSION CYTOKINES
Hematopoietic stem cell	SCF; TPO	Flt3-Ligand; SCF; TPO; IL-3; IL-6

THE INNATE IMMUNE SYSTEM			THE ADAPTIVE IMMUNE SYSTEM		
	DIFFERENTIATING CYTOKINES	SECRETED CYTOKINES		DIFFERENTIATING CYTOKINES	SECRETED CYTOKINES
Myeloid progenitor	IL-3; IL-6; EPO; GM-CSF; G-CSF		Lymphoid progenitor	IL-7	
Monocyte	GM-CSF; G-CSF		B cell progenitor	IL-3; IL-4; IL-6; IL-7; SCF	
Macrophage	IFN-γ; IL-6; IL-10; M-CSF	TGF-β; TNF-α; VEGF; IL-1β; IL-6; IL-10; IL-12	Plasma cell	IL-4; IL-5; IL-10; IL-21; TGF-β; IFN-γ	
Dendritic cell	Flt3-Ligand; GM-CSF; IFN-α; IL-4	IL-1α; IL-1β; IL-4; IL-6; IL-10; IL-12; TGF-β; IFN-α; IFN-γ	T cell progenitor	IL-2; IL-7; Notch	GM-CSF; TGF-β; TNF-α; IL-4; IL-6; IL-10; IL-12
Eosinophil	IL-3; IL-5; GM-CSF	TGF-β; VEGF; PDGF-BB; TNF-α; IL-1α; IL-1β; IL-2; IL-4; IL-5; IL-6; IL-8; IL-12; IL-13	Helper T cell	IL-2; IL-4; IL-6; IL-12; TGF-β; IFN-γ	* IFN-γ; TNF-α; TGF-β; IL-4; IL-5; IL-6; IL-9; IL-10; IL-13; IL-17; IL-21; IL-22
Basophil	IL-3; IL-6; GM-CSF; G-CSF	TNF-α; IL-4; IL-6; IL-13	Cytotoxic T cell	IL-2; IL-5; IL-7; IL-12	IFN-γ; TNF-α; TNF-β; IL-2; sFas Ligand
Mast cell	IL-3; IL-6; GM-CSF; G-CSF	TNF-α; GM-CSF; IL-3; IL-4; IL-5; IL-6; IL-8; IL-13			
Neutrophil	IL-6; GM-CSF; G-CSF; SCF	APRIL; RANKL; TNF-α; TGF-β; VEGF; IL-1α; IL-1β; IL-6; IL-12; IL-18; IL-21			
NK cell	IL-15	GM-CSF; IFN-γ; TNF-α; MIP-1α; MIP-1β; IL-5; IL-10; IL-17; IL-22			

Note - The list of the differentiating and secreted cytokines is partial.
* - Secreted by different subsets of Th cells.

Source: https://lab-a-porter.com/2019/12/cells-of-the-immune-system/

Top 25 Autoimmune Diseases

Disease	Therapeutic Area	Impact on Patients	US	G8 Prevalence	Unmet Need
Psoriasis	Dermatology	Moderately to highly debilitating	5,300,000	17,760,000	Modest
Grave's Disease	Endocrinology	Moderately debilitating	3,300,000	10,800,000	High
Celiac Disease	Gastroenterology	Moderately debilitating	2,800,000	8,800,000	High
Autoimmune thyroiditis	Endocrinology	Moderately debilitating	2,500,000	5,900,000	Medium
Rheumatoid Arthritis	Rheumatology	Moderately debilitating	1,500,000	5,000,000	Modest
Psoriatic Arthritis	Rheumatology	Moderately debilitating	1,325,000	4,440,000	Modest
Vitiligo	Dermatology	Moderately debilitating	640,000	3,630,000	High
Inflammatory Bowel Disease	Gastroenterology	Moderately to highly debilitating	1,150,000	3,220,000	High
Ankylosing Spondylitis	Rheumatology	Moderately debilitating	1,020,800	2,918,100	Modest
Autism	Neurology	Severely debilitating	1,250,000	2,440,000	High
Deep Vein Thrombosis	Cardiology	Severely debilitating	900,000	2,362,500	Medium
Sjogren's Syndrome	Rheumatology	Moderately debilitating	640,000	1,680,000	Medium
Systemic Lupus Erythematosus	Rheumatology	Severely debilitating for many	480,000	827,000	Medium
Hidradenitis suppurativa	Dermatology	Moderately debilitating	230,000	626,750	Medium
ANCA Associated Vasculitis	Renal	Highly Debilitating	134,400	366,240	High
Scleroderma	Rheumatology	Severely debilitating	300,000	300,000	High
Myasthenia Gravis	Neurology	Severely Debilitating	60,000	225,000	Modest
Bullous Pemphigoid	Dermatology	Sometimes debilitating in adults	38,400	138,000	Medium
Thrombocytopenic Purpura (ITP)	Hematology	Sometimes debilitating in adults	55,000	128,000	Modest
Autoimmune Hepatitis	Hepatology	Can be debilitating	48,000	126,000	High
CIDP	Neurology	Highly Debilitating	40,000	120,000	High
Diabetes Type I	Endocrinology	Highly Debilitating	35,000	115,000	High
Lupus Nephritis	Nephrology	Highly debilitating	63,000	105,000	Medium
Microscopic colitis	Gastroenterology	Highly Debilitating	38,400	104,640	High
Pemphigus vulgaris	Dermatology	Highly Debilitating	35,000	90,000	High

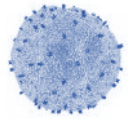
Source: Stifel Research

Immunology:
Drug Development
and Pharmacology

Core Areas for Development of Autoimmune Drug Candidates

1 Adaptive Immune System: T-Cell Driven Autoimmunity

- T-cells can directly kill foreign invaders via CD8+ cells while Treg cells (e.g., $CD4$'s) can help T-cell activity and drive the B-cell system
- Sometimes T-cells or related parts of the system attack self causing diseases like psoriasis or rheumatoid arthritis
- Areas of interest includes drug for inflammatory cytokines triggered by T-cells and associated co-stimulatory domains.



2 Adaptive Immune System: B-Cell Driven Autoimmunity / Autoantibodies

- B-cells are responsible for the production of antibodies which can kill cells directly. They are primed by dendritic cells or antigen-presenting cells
- There are many B-cell mediated diseases where the body mistakenly attacks itself
- Key areas of development are for drugs that eliminate plasma cells and underlying antibodies.

3 Complement System

- The alternative system that complements the role of antibodies and phagocytes
- In this case, elements of the complement system attack the pathogen cell membrane
- There are a number of diseases where the body's complement system attacks itself

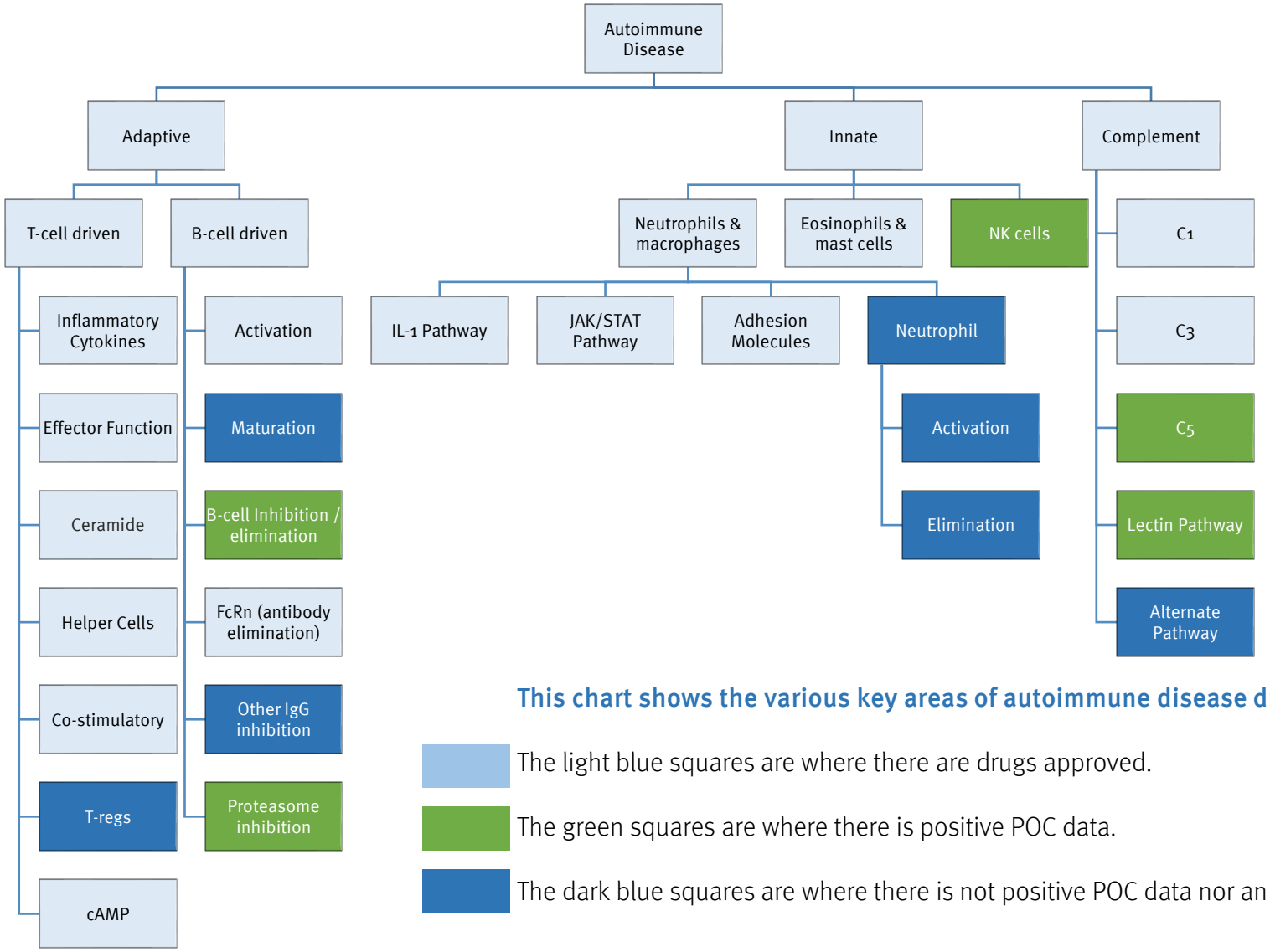
4 Innate Autoimmunity: Macrophages and Meutrophils

- Attacks invaders directly via macrophages and neutrophils without learning antigens. Neutrophils are responsible for more than two dozen autoimmune diseases
- There are also a number of pathologies that are directly linked to macrophages.

5 Innate autoimmunity: Eosinophils & Mast Cells

- Eosinophils are a subtype of mononuclear cells associated with allergy
- There are an emerging set of diseases where eosinophils / mast cells mistakenly attack self including asthma and atopic dermatitis
- Some of the highest potential future growth may emerge in this area

Autoimmune Disease Biology Dendrogram



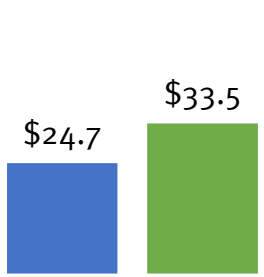
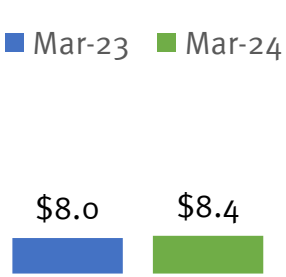
This chart shows the various key areas of autoimmune disease drug research:

The light blue squares are where there are drugs approved.

The green squares are where there is positive POC data.

The dark blue squares are where there is not positive POC data nor an approved drug

B-Cell Driven Autoimmunity Sector the Most Highly Valued in the Market Today

(in $bn)	T-Cell Driven Autoimmunity	B-Cell Driven Autoimmunity	Complement System	Innate Autoimmunity / Macrophages and Neutrophils	Innate Autoimmunity / Eosinophils & Mast Cells
Combined EV of US Public Immunology Companies under Various Pathways					
Return Last Twelve Months	9%	36%	6%	3%	61%
# of Public Cos[1]	17	11	7	8	6[2]
IPO/reverse merger (RM) L12M (% return since IPO/RM)	ACELYRIN IPO: May 2023 Stock price down 66%	Cartesian THERAPEUTICS RM: Nov. 2023 Stock price down 17%	DIANTHUS THERAPEUTICS RM: Sep 2023 Stock price up 125%	TOURMALINE RM: Oct 2023 Stock price up 256%	Q32 BIO RM: Nov. 2023 Stock price up 5%
Notable M&A	Prometheus Biosciences / MERCK $10.8bn (Apr. 2023)	Momenta / Johnson&Johnson $6.5bn (Aug. 2020)	IVERIC bio / astellas $5.9bn (Apr. 2023)	nimbus THERAPEUTICS / Takeda $4.0bn (Dec. 2022)	Dermira / Lilly $1.1bn (Jan. 2020)

Source: Stifel analysis of press releases and CapitalIQ as of 3/8/2024. Post IPO/RM returns computed to 2/29/2024; Notes: 1. Include public immunology companies across countries; 2. Includes Q32, merger with Homology pending; 3. For the comparison between 2023 and 2024 we excluded companies that were not public or did not exist in 2023 to avoid upward bias.

Select Public Inflammation and Immunology Biopharmas

Despite frequent M&A takeouts, there remain 17 publicly traded I&I biopharmas with an enterprise value of $1 billion or more

Company	Ticker	Lead Pipeline Drug	MOA of Lead Drug	Field of Immunology	Last Completed Stage of Testing	Enterprise Value ($mm)	Market Cap ($mm)	Change in Market Cap (Last 12 Months)	Change in Market Cap (YTD)
argenx	ARGX	Efgartigimod	FcRn	B-Cell	Commercial	$19,995	$23,124	20.9%	3.1%
Apellis	APLS	SYFOVRE	C3	Complement	Commercial	$7,187	$7,431	3.6%	4.8%
Immunovant	IMVT	Batoclimab	FcRn	B-Cell	Phase 3	$3,914	$4,604	129.1%	-24.5%
Apogee Therapeutics	APGE	APG777	IL-13 (Long life)	Innate: Eosinophils	Phase 1	$3,028	$3,421	NA	141.6%
Remegen	SEHK:9995	Telitacicept	April/BAFF	B-Cell	Phase 3	$2,955	$2,956	-38.9%	-25.8%
Roivant Sciences	ROIV	RVT-3101	JAK/STAT	T-Cell	Phase 2	$2,937	$8,606	48.3%	-4.7%
Celldex Therapeutics	CLDX	Barzolvolimab	cKIT	Innate: Eosinophils	Phase 2	$2,665	$3,086	56.4%	42.3%
Moonlake Therapeutics	MLTX	Sonelokimab	il-17	T-Cell	Phase 2	$2,378	$2,868	244.8%	-20.8%
TG Therapeutics	TGTX	BRIUMVI	CD20	B-Cell	Commercial	$2,323	$2,429	25.4%	0.6%
Kymera Therapeutics	KYMR	KT-474	IRAK4	Innate: Macrophages	Phase 1	$2,306	$2,658	62.8%	88.1%
Alpine Immune Sciences	ALPN	Povetacicept	April/BAFF	B-Cell	Phase 2	$2,104	$2,287	589.0%	106.9%
Kyverna Therapeutics	KYTX	KYV-101	CD19 CAR-t	B-Cell	Phase 1	$1,346	$1,233	NA	NA
Kiniksa	KNSA	ARCALYST	il-1 TRAP	Innate: Macrophages	Commercial	$1,275	$1,469	75.7%	19.1%
Spyre Therapeutics	SYRE	SPY001	α4β7 Int (Long life)	T-Cell	Preclin	$1,217	$1,371	NA	76.9%
Arcutis Biotherapeutics	ARQT	Zoryve	PDE4	T-Cell	Commercial	$1,216	$1,282	73.6%	320.5%
Morphic Therapeutic	MORF	MORF-057	α4β7 Int (Oral)	T-Cell	Phase 2	$1,158	$1,860	11.2%	29.5%
Tourmaline Bio	TRML	TOUR006	IL-6	Innate: Macrophages	Phase 2	$1,122	$1,071	NA	101.2%
Viridian	VRDN	VRDN-001	IGF-R1	Innate: Macrophages	Phase 2	$953	$1,201	-1.4%	4.9%
ABIVAX	ABVX	Obefazimod	mir-124 agonist	T-Cell	Phase 2	$814	$894	219.3%	31.4%
Cabaletta Bio	CABA	CABA-101	CD19 CAR-t	B-Cell	Phase 1	$803	$963	366.7%	-1.0%
Pharming	PHARM	RUCONEST	C1	Complement	Commercial	$743	$778	-0.5%	2.0%
AnaptysBio	ANAB	Rosnilimab	PD1 Agonist	T-Cell	Phase 1	$576	$659	5.5%	15.8%
Dianthus	DNTH	DNTH103	C1 (Long life)	Complement	Phase 2	$548	$737	NA	378.1%
Aurinia Pharma	AUPH	Lupkynis	Calcineurin Inhibitor	T-Cell	Commercial	$533	$785	-37.3%	-39.2%
Omeros	OMER	Narsoplimab	MASP-2	Complement	Phase 3	$431	$275	34.6%	33.9%
Ventyx Biosciences	VTYX	VTX-958	NLRP3	Innate: Macrophages	Phase 2	$348	$588	-73.5%	303.1%
Cartesian Biosciences	RNAC	Descartes-08	BCMA CAR-t	B-Cell	Phase 1	$338	$104	NA	-3.1%
RAPT Therapeutics	RAPT	RPT193	CCR4	T-Cell	Phase 2	$164	$316	-62.3%	-63.0%
Immunic	IMUx	IMU-838	DHODH Inhibitor	T-Cell	Phase 2	$92	$138	86.7%	103.2%
Immix Biopharma	IMMX	NXC-201	BCMA CAR-t	B-Cell	Phase 1	$62	$82	227.3%	-40.3%
Acelyrin	SLRN	Izokibep	IL-17 Minibody	T-Cell	Phase 2	-$59	$728	NA	0.3%
Aclaris Therapeutics	ACRS	Zunsemetinib	MK2	Innate: Macrophages	Phase 2	-$78	$100	-81.0%	34.5%
					Median:	**$1,140**	**$1,217**	**41.5%**	**15.8%**

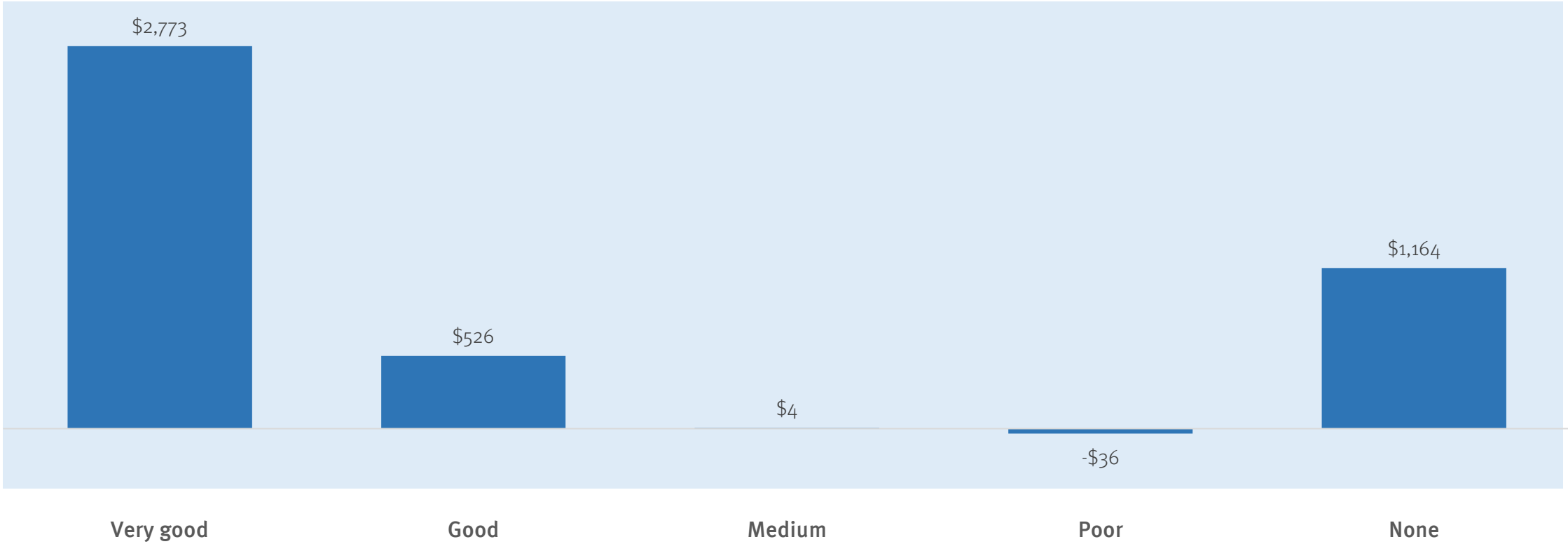
Source: Stifel analysis of press releases and CapitalIQ as of 3/8/2024.

Valuations Much Higher for I&I Companies with High Quality Data

There is a sharp drop off in value for companies that go from a “very good” dataset to one that is “good”. Good means some chance to meet or beat the standard of care for an indication while “very good” means the company has demonstrated a high likelihood of beating the standard of care. Interestingly, companies like Spyre that do not yet have data still command high valuations based on mechanistic / inferential analysis.

Average Enterprise Value of an Immunology Biopharma Company by Quality of Efficacy Data

March 8, 2024 ($ millions), N=49

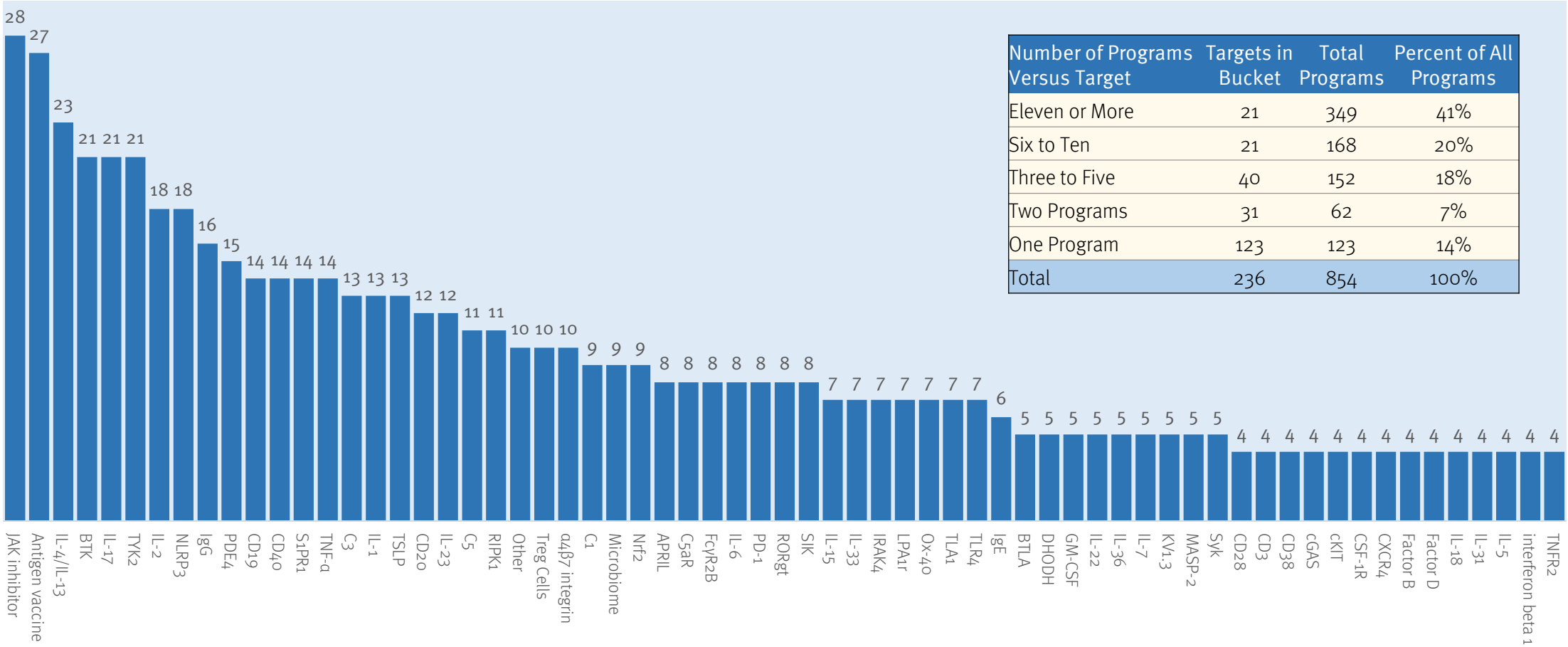


Notes: These data are sourced from CapitalIQ and based on Stifel research on the dataset quality for a company’s lead asset. We classified datasets that indicated a high probability that the drug would meaningfully improve on the standard of care for a disease as “very good”. We classified “good” data as data that might beat the standard of care. Medium data was data that was unlikely to beat the standard of care, was very early or came from a study with a mixed signal. Poor data reflects situations where a drug did not perform well at all in a clinical trial.

Significant Crowding Within Immunology Target Space

We track over 800 pipeline programs in the Stifel immunology database. Strikingly, over 60% of programs are in fields with six or more programs in development. On the other hand, there are 123 target fields with only a single program in development at present.

Count of Immunology Programs by Target (4 or More Programs in Development, March 2024)



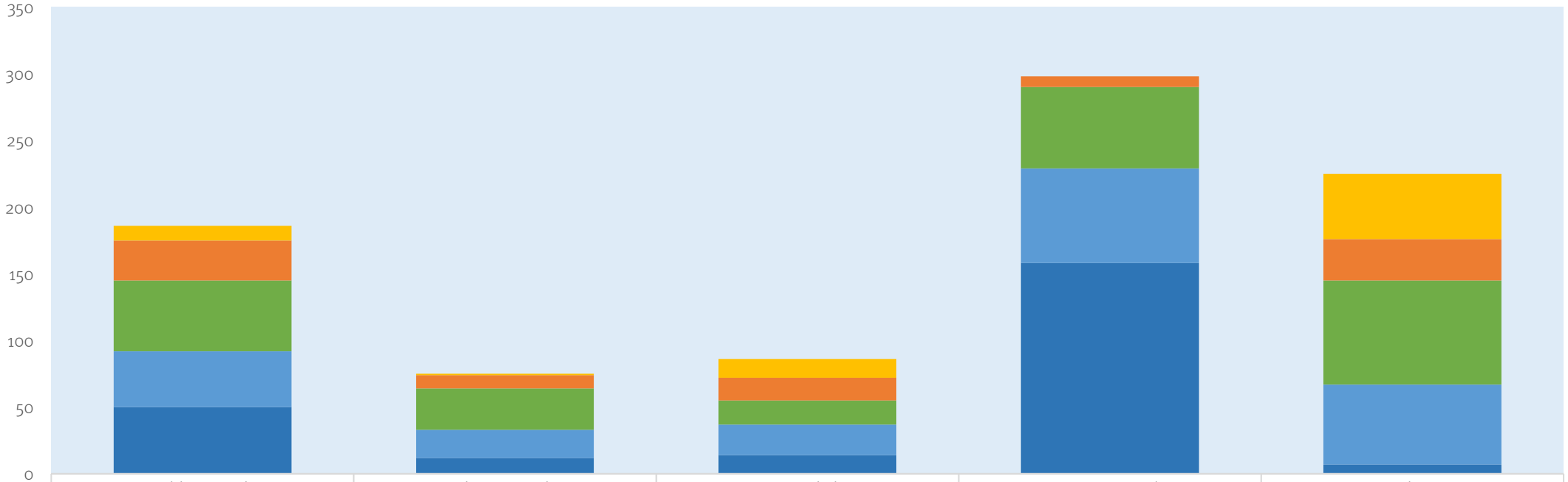
Number of Programs Versus Target	Targets in Bucket	Total Programs	Percent of All Programs
Eleven or More	21	349	41%
Six to Ten	21	168	20%
Three to Five	40	152	18%
Two Programs	31	62	7%
One Program	123	123	14%
Total	236	854	100%

Source: Analysis of Stifel database of autoimmune and immunology pipeline programs, March 2024. The Stifel database was compiled from Google searches, search of EvaluatePharma, search of DealForma, internal Stifel documents and Wall Street research.

Where Are Immunology Pipeline Programs by Company Type?

Private biotechs house the most I&I pipeline programs (by a wide margin). However, most private biotech programs are Phase 1 or earlier. Commercial pharma, in contrast, has the most marketed products. Less than 20% of I&I programs are held by public biotechs. More than half of public biotech programs are Phase 2 or later.

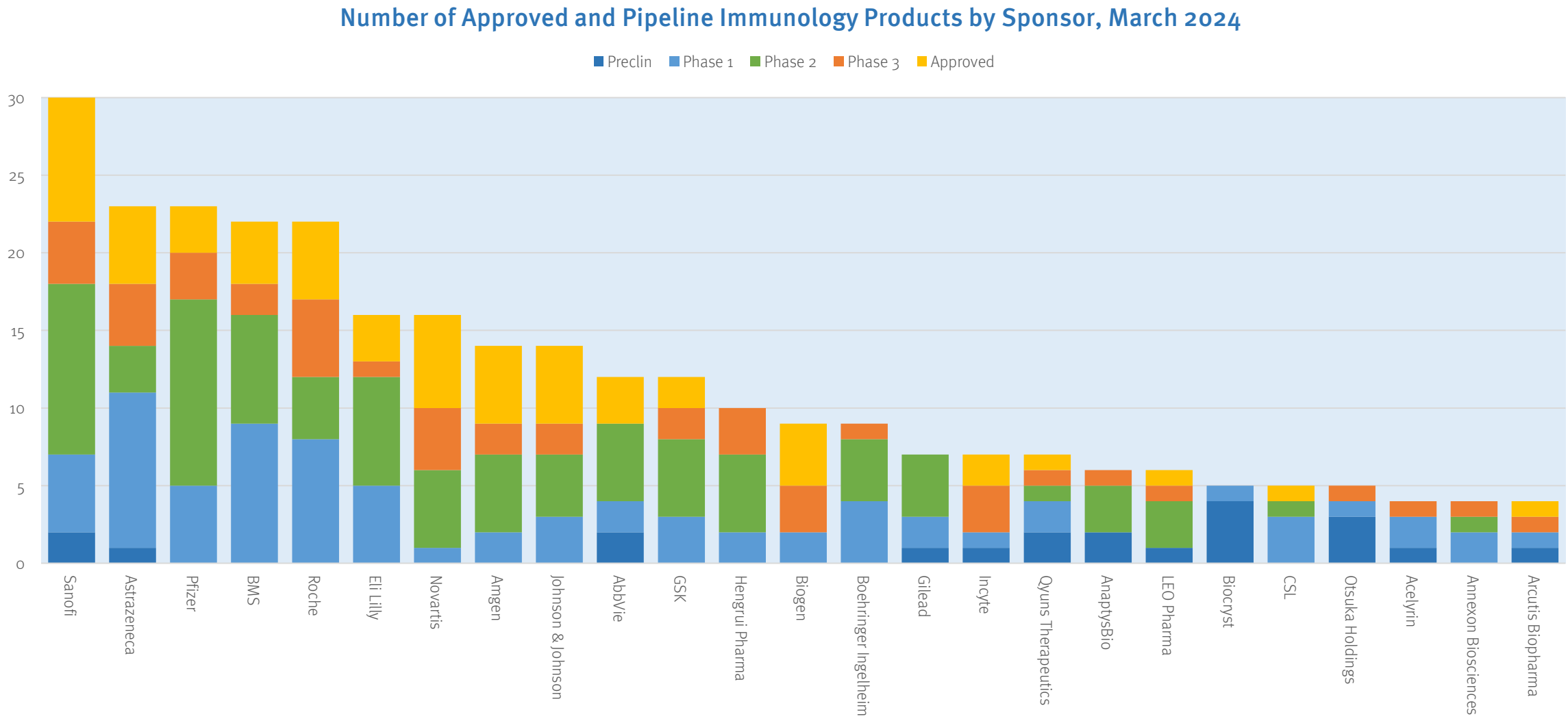
Distribution of Immunology Pipeline by Type of Company and Stage of Development, March 2024 (N=878)



	Public Biotech	China Biotech	Commercial Pharma	Private Biotech	Big Pharma
Marketed	11	1	14	0	49
Phase 3	30	10	17	8	31
Phase 2	53	31	18	61	78
Phase 1	42	21	23	71	60
Preclinical	50	12	14	158	7

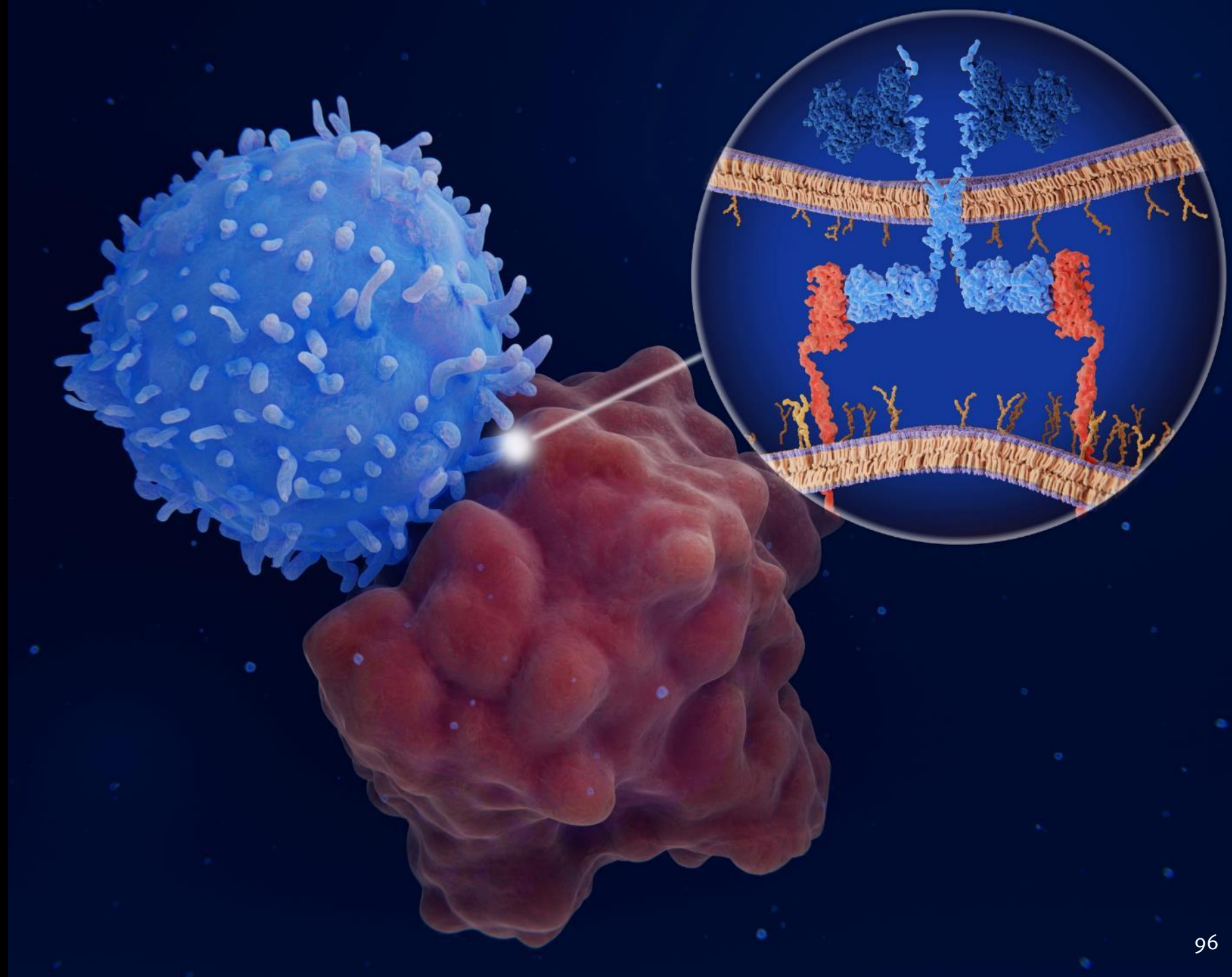
Source: Analysis of Stifel database of autoimmune and immunology pipeline programs, March 2024.

Sanofi Has the Most Immunology Products in the Market and in Development by Far



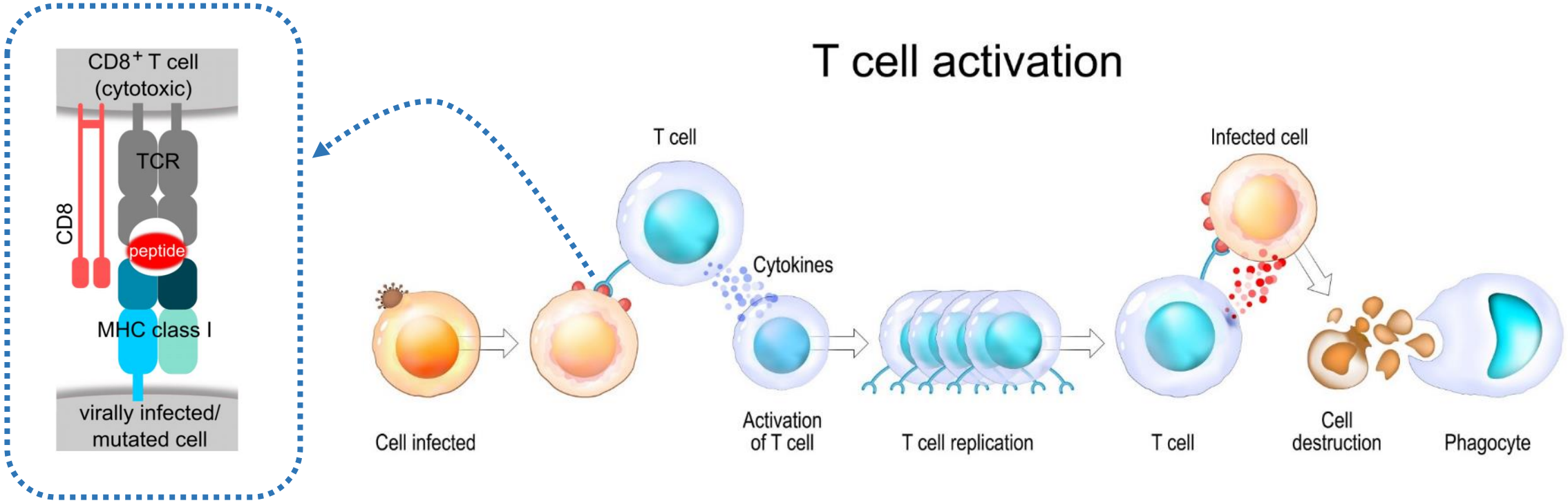
Source: Analysis of Stifel database of autoimmune and immunology pipeline programs, March 2024.

Immunology:
T-Cell System
Autoimmunity



T-Cells are a Core Part of the Adaptive Immune System

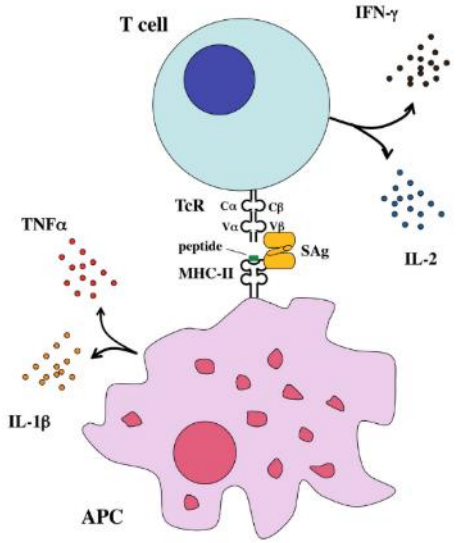
T cells are part of the immune system and develop from stem cells in the bone marrow. They help protect the body from infection and may help fight cancer. The chart below illustrates the classical T-cell activation pathway.



The T-cell receptor known as the TCR binds to its cognate antigen/MHC I pair triggering the activation of resident T-memory cells – which are then replicated for use against infected cells.

Source: https://www.researchgate.net/figure/MHC-class-I-and-class-II-and-their-role-as-mediators-during-antigen-presentation-and_fig1_280663544

T-Cell System Biology



T-cells are activated by two types of signals. The first is when dendritic cells or antigen presenting cells (APCs) interact with a TCR (T-cell receptor) via an MHC Class II complex. The second signal occurs when the T cell and APC communicate by co-activating proteins when these cells interact. These proteins include CD28, CD80/86, TNF, IL-33, IL-2, INF γ and IL-15. CTLA-4 prevents the binding of CD28 to CD80/86 which is important in preventing Th activation. One of the key effects of co-activation is to induce the differentiation of T-cells into T-helpers (CD4's) and T effector cells (CD8+'s).

Source of chart: Proft and Fraser, Streptococcal Superantigens: Biological properties and potential role in disease, 2016.

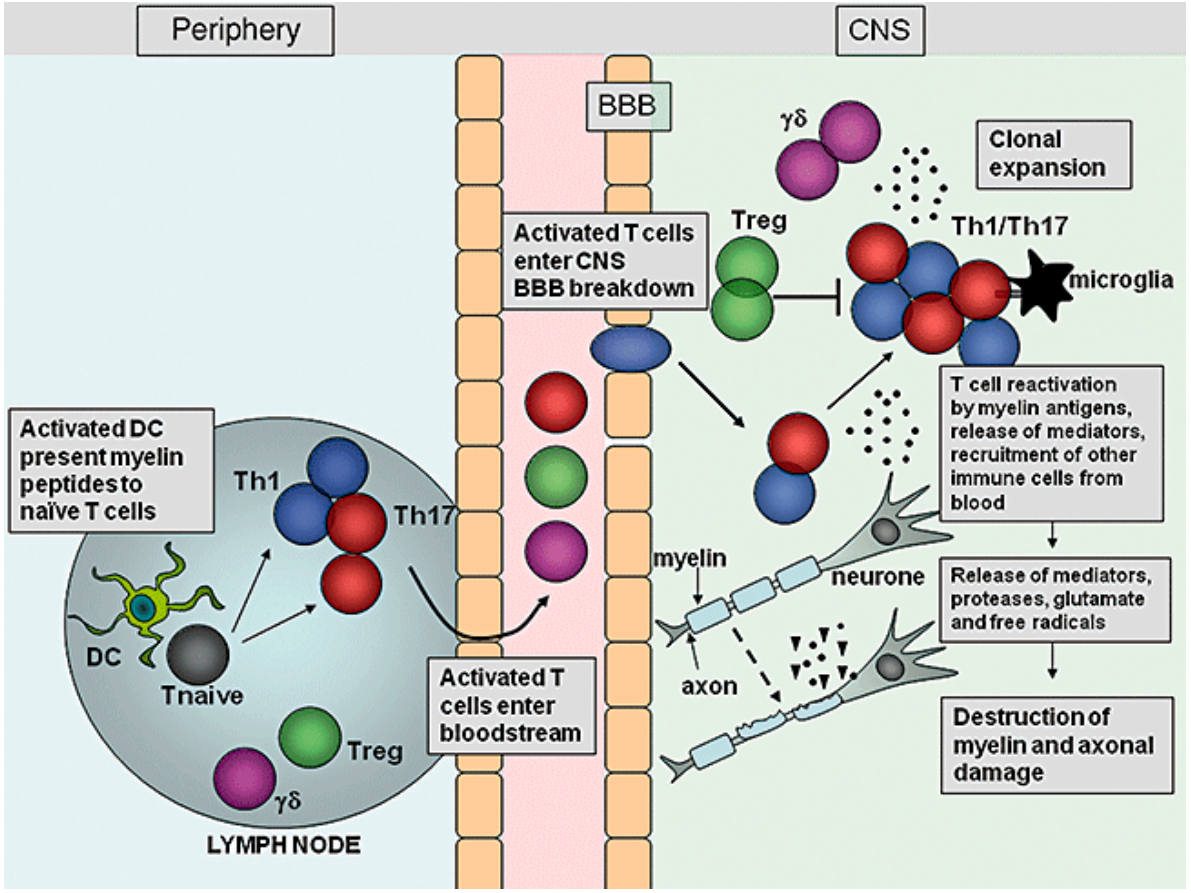
T-Cell Targets in Autoimmunity Dendrogram

There are multiple links between T-cell behavior and autoimmunity including the effect of inflammatory cytokines, T-cell effector function, T-cell interaction with phospholipids and ceramide, the effect of T-helper cells, co-stimulatory receptors and cAMP mechanisms.

Current Thinking on Multiple Sclerosis Pathology

Current thinking describes multiple sclerosis as a T-cell driven disease where clonally expanded Th1/Th17's attack the myelin. These cells are differentiated from naïve T-cells via interaction with dendritic cells.

Fletcher JM, Lalor SJ, Sweeney CM, Tubridy N, Mills KH, "T cells in multiple sclerosis and experimental autoimmune encephalomyelitis," *Clin Exp Immunol.* 2010;162(1):1–11.

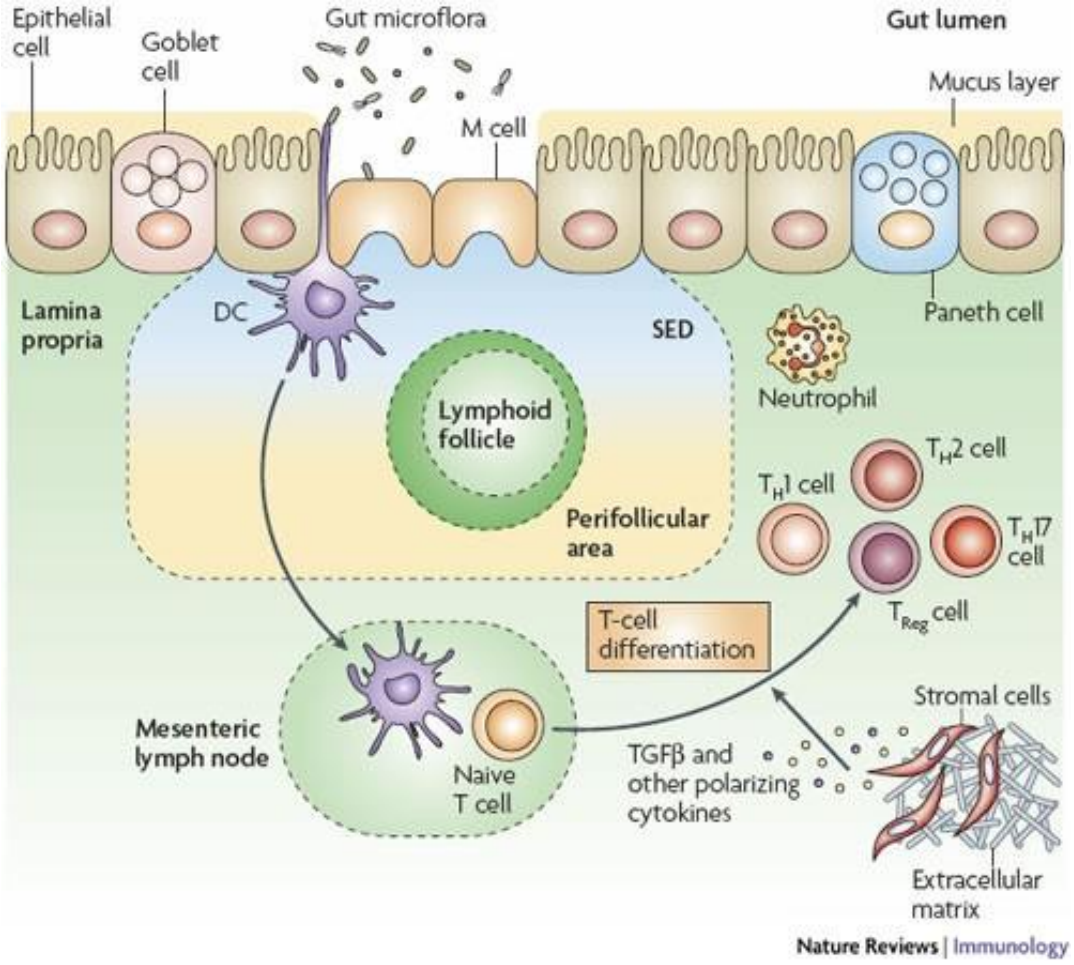


"Migration and effector function of T cells in the central nervous system (CNS) during experimental autoimmune encephalomyelitis (EAE). After immunization with myelin antigens, dendritic cells (DC) are activated in the lymph nodes by Toll-like receptor (TLR) agonists and present myelin antigen to naive T cells. The activated myelin-specific T cells enter the bloodstream and traffic to and enter the CNS. Breakdown of the blood–brain barrier (BBB) occurs, allowing recruitment of other inflammatory cells into the CNS. T cells entering the CNS encounter their cognate myelin antigens and become reactivated by local APC. T cells expand and release inflammatory mediators which help recruit other immune cells to the site of inflammation. Activation of local microglial cells and infiltrating cells results in production of proteases, glutamate, reactive oxygen species and other cytotoxic agents which promote myelin breakdown. Damage to the myelin sheath surrounding axons is followed by axonal damage and neurological impairment."

Current Thinking on IBD Pathology

Current thinking describes IBD as a T-cell driven disease where clonally expanded Th1/Th17's attack the gut epithelial cell antigens. These cells are differentiated from naïve T-cells via interaction with dendritic cells. Treg's also need to fail to restrain Th1's in the process.

Cho JH. The genetics and immunopathogenesis of inflammatory bowel disease. *Nat Rev Immunol.* 2008;8(6):458-466.



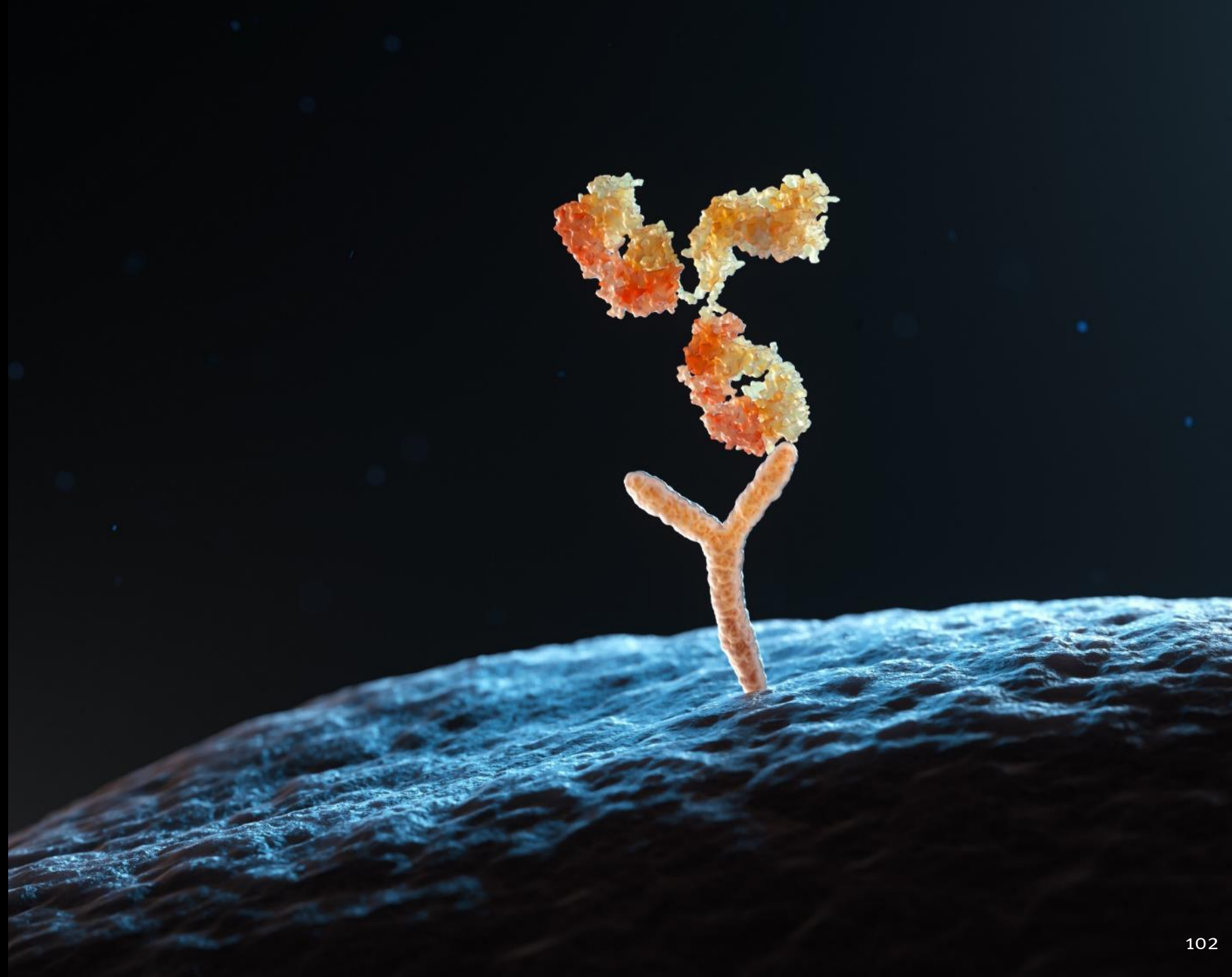
IBD is seen as a disease where dendritic cells incorrectly identify gut epithelial cell antigens as foreign objects and then sensitize t-cells to lead an attack on such cells. This attack is accomplished by the failure of Treg cells to balance Th1's vs. Th2's.

This, in turn, leads to Th1/Th17 cell attack on the epithelial lining of the gut.

T-Cell Driven Autoimmunity Pipeline is Rich and Diverse

Source: Stifel research, DealForma, press releases

Immunology:
B-Cell System
Autoimmunity



B-Cells are a Core Part of the Adaptive Immune System

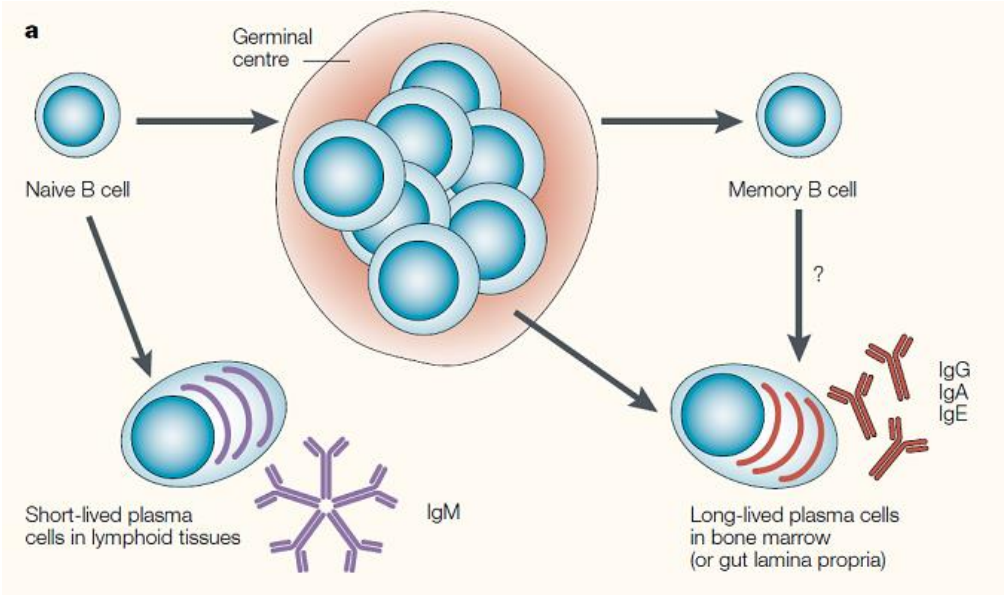
B-cells are a type of white blood cell that make infection-fighting proteins called antibodies. B-cells are an important part of the immune system, the body's defense against harmful pathogens (viruses, bacteria and parasites) that enter the body and make one ill.

B-cells and T-cells are a specific type of white blood cell called lymphocytes. Lymphocytes fight harmful invaders and abnormal cells, like cancer cells. T-cells protect a person by destroying pathogens and sending signals that help coordinate your immune system's response to threats. B-cells make antibodies in response to antigens (antibody generators). Antigens are markers that allow your immune system to identify substances in the body, including harmful ones like viruses and bacteria.

There are two main types of B-cells: plasma cells and memory cells. Both types help protect from infection and disease.

Plasma cells: Plasma cells release antibodies in response to antigens. Once a B-cell becomes a mature plasma cell, it can release up to 2,000 antibodies per second. Plasma cells are also called plasmacytes or effector cells. They have a shorter lifespan than memory cells.

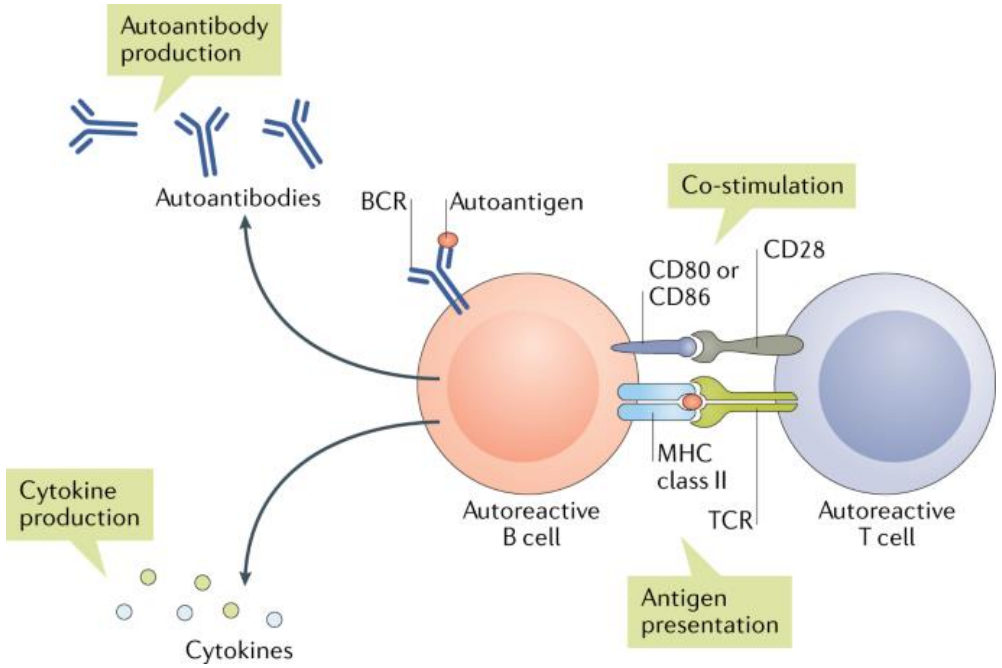
Memory cells: Memory cells remember particular antigens. Thus, if they appear in the body in the future, the immune system can mount a defense quickly. While plasma cells fight bodily invaders by producing antibodies, memory cells help the immune system fight in the future. For example, most vaccines work because they expose the immune system to antigens that memory cells remember.



Nature Reviews Immunology 2, 60-65,

B-cells can differentiated into memory cells that remember antigen or long-lived plasma cells that release IgG, IgA and IgE antibodies. They can also differentiate into short-lived plasma cells that release IgM antibodies. Once a B-cell becomes a mature plasma cell, it can release up to 2,000 antibodies per second. Plasma cells are also called plasmacytes or effector cells. They have a shorter lifespan than memory cells.

B-Cell System Biology



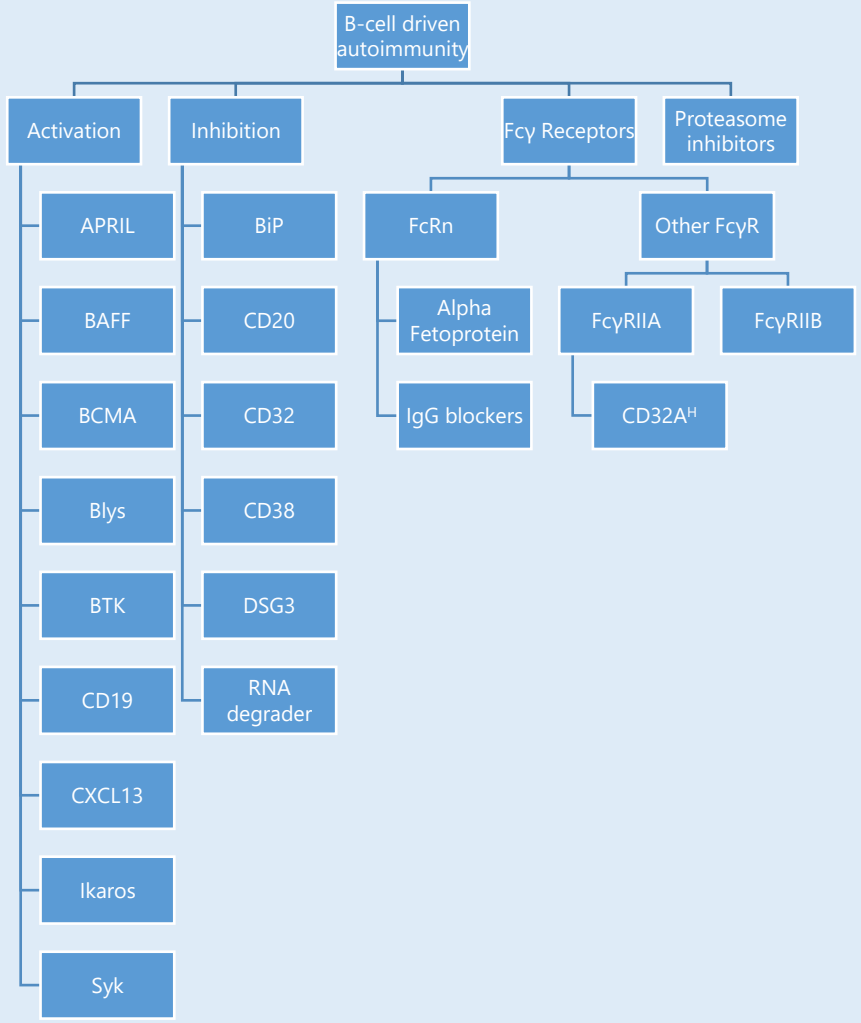
Central B cell functions, including antibody production, antigen presentation and T cell help via co-stimulation and/or cytokine secretion, can all contribute to the pathogenesis of autoimmune diseases.

Interest in understanding the mechanisms by which B cells contribute to autoimmunity and autoimmune tissue destruction was sparked in part by the unanticipated efficacy of B cell-depleting anti-CD20 monoclonal antibodies in treating autoimmune diseases including rheumatoid arthritis (RA), anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis and multiple sclerosis.

Source of chart: https://www.nature.com/articles/s41584-019-0211-0

B-Cell Targets in Autoimmunity Dendrogram

There are multiple links between B-cell behavior and autoimmunity including the B-cell activation and inhibition. Other MOA's involve proteasome inhibitors and interactions between Fc gamma receptors and antibodies.

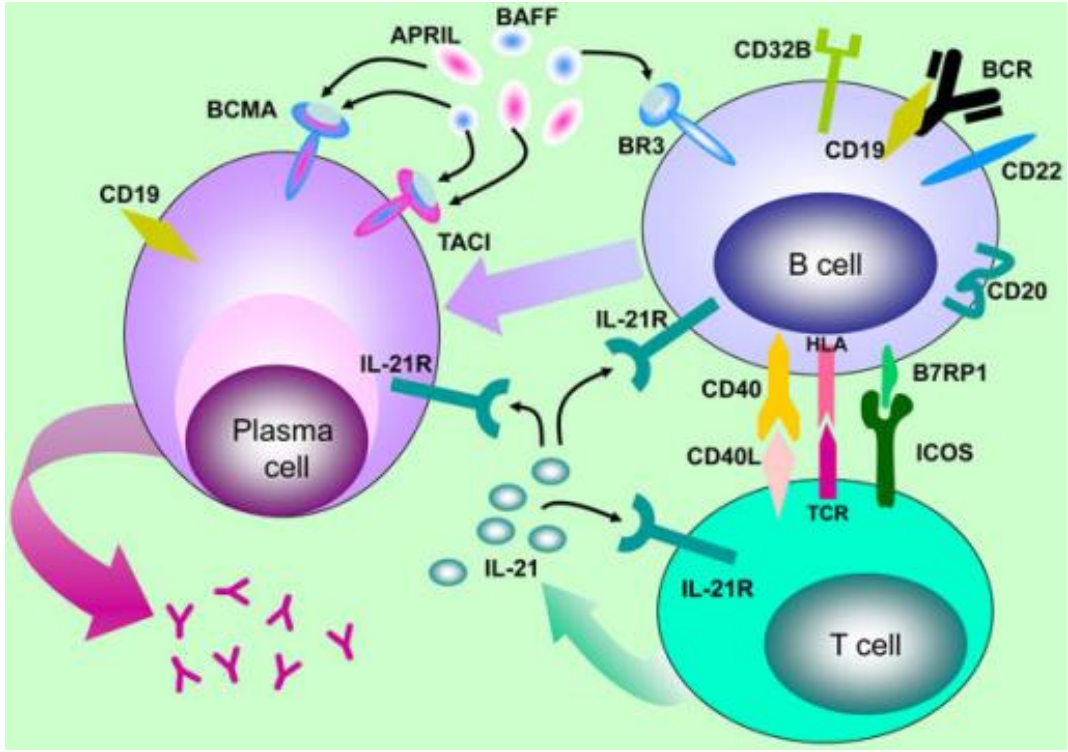


B-Cell Targeting to Control Autoimmune Disease

B-cell antigens and cytokines targeted by biologics in clinical development. Schematic representation of B-cell/T-cell interaction and differentiation of activated B cells into antibody secreting plasma cells. B cells presenting antigen to T cells via HLA receive co-stimulatory signals from T-cell-expressed CD40 ligand (CD40L).

CD4 T cells, in particular T follicular helper (TFH) cells, in turn receive activating signals from the B-cell-expressed ICOS ligand B7RP-1. Class switch recombination by B cells and plasma cell differentiation are critically dependent on IL-21 and co-stimulation through the CD40/CD40L pathway.

The two TNF family members B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL) provide survival signals by triggering their respective receptors expressed on B cells (BAFF receptor BR3 and transmembrane activator and calcium-modulating ligand interactor (TACI) on memory B cells) and plasma cells (BAFF/APRIL receptors B-cell maturation (BCMA) and TACI). B cells can also be directly targeted by antibodies against B-cell restricted antigens, such as CD20, CD22, and CD19. See text for additional details. BCR, B-cell receptor; TCR, T-cell receptor.



Plasma B cells are most recognizable for their extended lifespan as well as their ability to secrete large amounts of antibodies thus positioning this cell type as a key component of humoral immunity. Plasma B-cell activity is heavily impacted by from other B-cells which in turn have numerous receptors that receive signals, particularly from T-cells. These signals can be characterized as variously activating or inhibitory. Much of B-cell pharmacology today involves the modulating of this signaling activity.

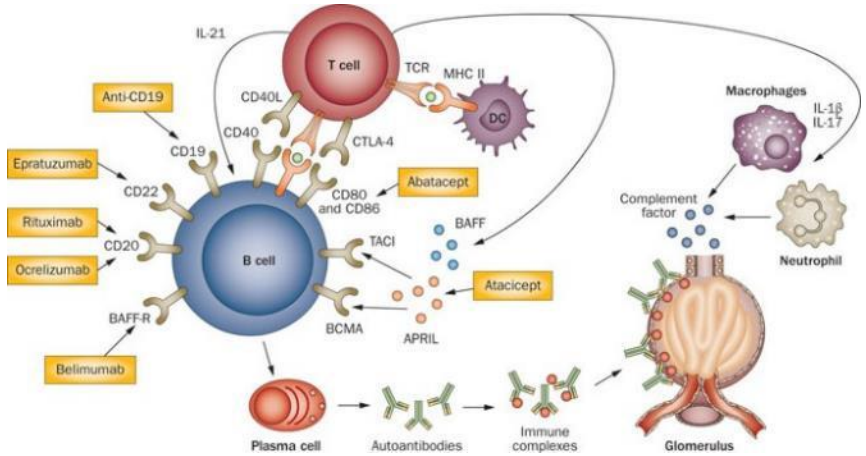
Source: B-cell targeted therapeutics in clinical development, *Arthritis Research and Therapy*, 2013.

Current Thinking on Lupus Nephritis Pathology

B cells are central to the pathogenesis of SLE and are, therefore, an attractive therapeutic target. B-cell depletion has been used successfully to treat related autoimmune diseases, such as rheumatoid arthritis and antineutrophil cytoplasmic antibody-associated vasculitis.

Ramos-Casals M, Sanz I, Bosch X, Stone JH, Khamashta MA. B-cell-depleting therapy in systemic lupus erythematosus. *Am J Med.* 2012;125(4):327-336.

"Systemic lupus erythematosus (SLE) is an autoimmune disease that is clinically heterogeneous and affects multiple organs. Lupus nephritis is the most frequent severe manifestation of SLE. Conventional immunosuppressive therapy has increased the life expectancy of patients diagnosed with lupus nephritis, but only 70–80% of patients respond to this treatment and its adverse effects are considerable. B cells are central to the pathogenesis of SLE and are, therefore, an attractive therapeutic target. B-cell depletion has been used successfully to treat other autoimmune diseases, such as rheumatoid arthritis and antineutrophil cytoplasmic antibody-associated vasculitis, and many case reports and small nonrandomized trials of B-cell-depleting agents in patients with lupus nephritis have reported positive results. By contrast, two large placebo-controlled trials designed to investigate the efficacy of the B-cell-depleting agents rituximab and ocrelizumab as a treatment for lupus nephritis, failed to meet their primary efficacy end points (LUNAR and BELONG, respectively)."



B-cell therapies are designed to eliminate either the majority of B cells (general depletion) or only some B-cell populations (selective depletion). In both cases, depletion is achieved through 2 principal mechanisms:

1. Direct killing by monoclonal antibodies against B-cell surface molecules CD19, CD20 (rituximab, ocrelizumab), and CD22 (epratuzumab). The most widely tested category of anti-B-cell agents is anti-CD20 antibodies, which induce a broad and deep B-cell depletion but have only a modest effect on LN.
2. Attrition due to inhibition of B-cell survival factors BLyS (belimumab) and APRIL (atacicept). Belimumab has a significantly more restricted and attenuated B-cell effect by blocking the essential survival effect of BLyS. Atacicept induces the depletion of a significantly larger swathe of B cells and plasma cells, although this powerful effect also may increase the risk of severe infections. Results to date in LN have not been impressive with APRIL/BAFF inhibition.

Other potential strategies include complement inhibition, direct autoantibody inhibition, proteasome inhibition and innate immune system inhibition.

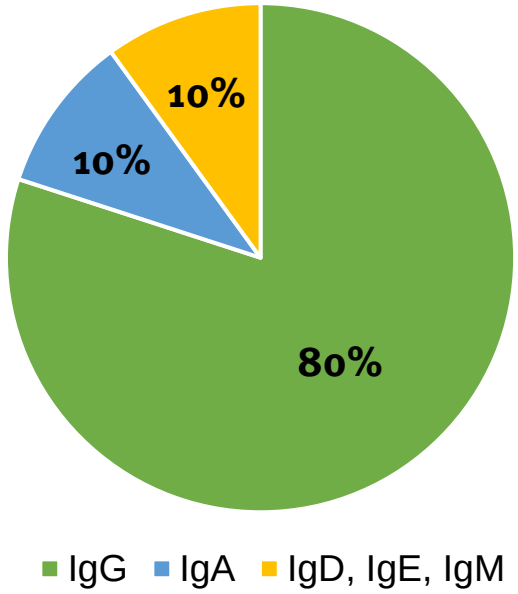
Current Pharmacologic Approaches to Autoantibodies

Blockers of FcRn IgG Binding Site	There are numerous companies that are focused on B-cell biology in one way or another. These include the FcRn companies such as Argenx which has achieved approval of efgartigimod for myasthenia gravis, ITP etc and Immunovant which is mid-stage. FcRn companies (including J&J, Alexion and UCB) focus on preventing the recycling of IgG thereby reducing the amount of all IgG by roughly 75%. While clinically attractive, these therapies may be risky for patients insofar as they also reduce levels of protective / beneficial antibodies.
Fc Gamma mAbs & Bispecifics	There is increasing recognition that the B and T-cell immune response is a coordinated one and that there is an opportunity to downregulate B-cells and T-cells. Several companies are exploring this idea with both IgG regulators and Fcγ regulating drugs. Some of the most exciting companies in the field of autoimmunity (e.g., ImUnity, Nuvig, Seismic) are to be found in this area.
B-Cell Ablation (Car-T)	Another class of companies such as AstraZeneca/Gracell, Cabaletta, Immix, Kyverna and Novartis are pursing the direct ablation of pathogenic B-cells with Car-T drugs. Cabaletta, for example, has reported remarkable reduction of advanced lupus using a CD-19 CAR-T therapy.
B-Cell Ablation (Antibodies)	Another class of companies such as TG Therapeutics develop therapeutics that ablate B-cells. Specifically, the therapies in development focus on cell surface markers that are heavily expressed on B-cells including CD19, CD20 and BCMA. The results from anti-CD20 antibodies (e.g., Rituxan®) are well understood and have pointed to important treatments for several autoimmune diseases and liquid tumors (caused by abnormal growth of B-cells).
IgG Degraders / IgG Traps	Yet another approach highlighted by Biohaven is to pursue extracellular degraders that remove pathogenic IgG. These therapies can be generalized IgG degraders or, instead, specific to a particular species of IgG. This type of therapy, therefore, has the potential to specifically target an autoimmune disease without impacting the overall antibody repertoire.

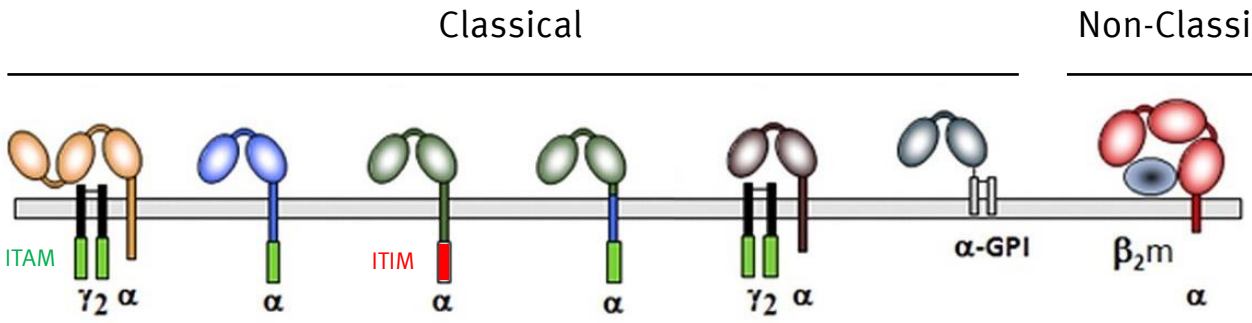
Source: Stifel Research

Fc Gamma Receptors that Bind IgG Antibodies

IgG is the most abundant antibody isotype



Fc gamma receptors (FcγRs) bind IgG antibodies



Name:	FcγR-I	FcγR-IIA	FcγR-IIB	FcγR-IIC	FcγR-IIIA	FcγR-IIIB	FcRn
IgG affinity:	**High**	Low	Low	Low	Low	Low	**High (pH<6.5)**
Function:	Activation	Activation	Inhibition	Activation	Activation	Unknown	Contextual

Investors and Physicians are Excited About High Potential of FcRn Inhibitors

Autoantibodies mediate a large number of autoimmune diseases

59
localized diseases

34
systemic diseases

Clinical trials with anti-FcRn inhibitors are focused on prototypical IgG mediated diseases

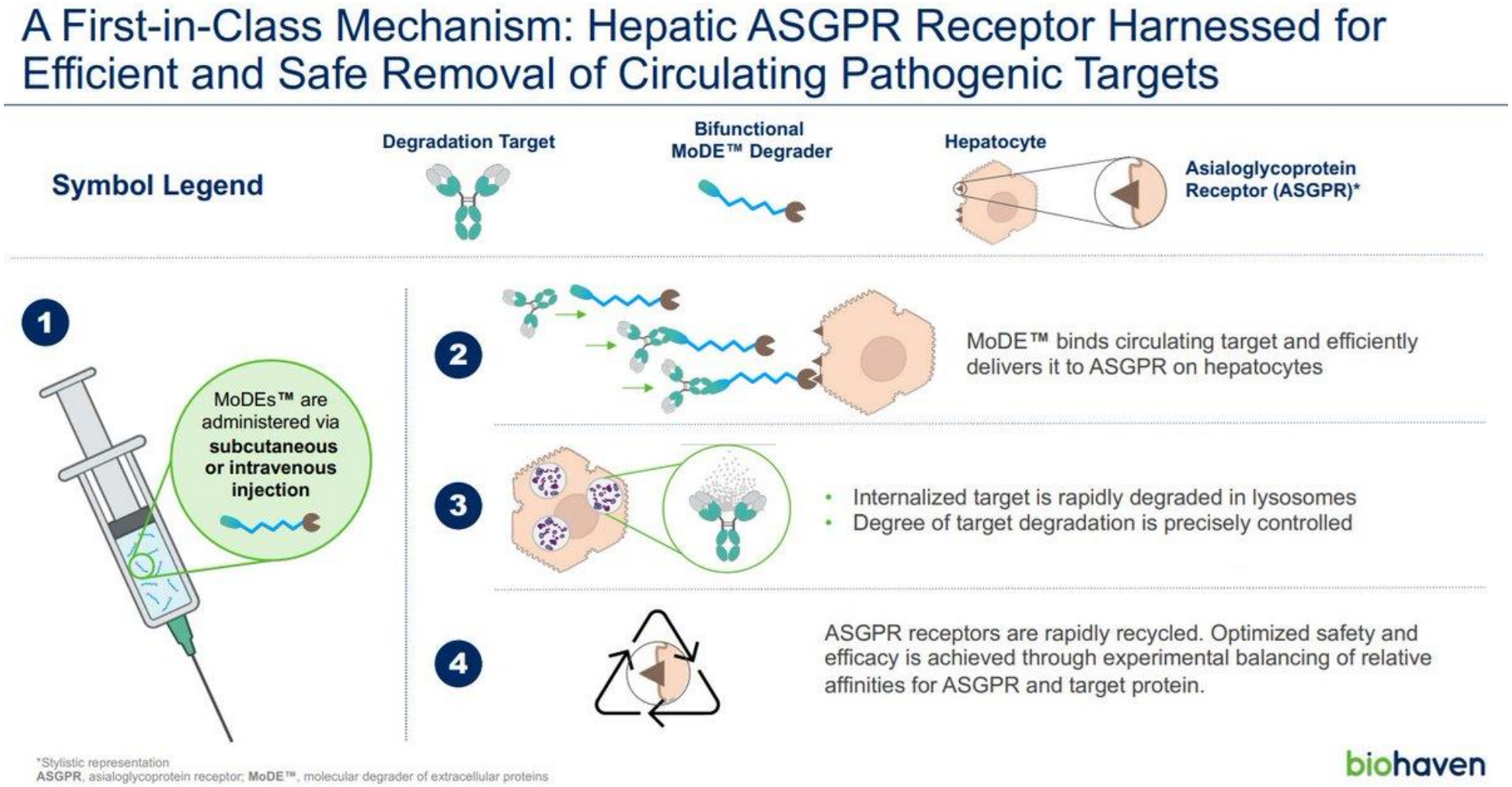
Compound/ manufacturer	K_D (nM)	Indication(s)	Phase	Study number	Citations
Rozanolixizumab (UCB7665; UCB Pharma)		MG	II or III	NCT04124965, NCT03971422, NCT03052751, 2016-002698-36	(101,102 103, 104)
IgG4 mAb	pH 6.0: 0.02	ITP	II or III	NCT02718716, NCT04224688, NCT04200456	
	pH 7.4: 0.03	CIDP	II	NCT04051944, NCT03861481	
			I	NCT02220153, NCT03859219	
Efgartigimod (ARGX-113; Argenx)		MG	II or III	NCT03770403, NCT03669588, NCT02965573	(105, 106)
IgG1 Fc fragment (M252Y/S254T/ T256E/H433K/N434F)	pH 6.0: 14	ITP	II or III	NCT03102593, NCT04188379, NCT04274452, NCT04225156	
	pH 7.4: 320	Pemphigus (PV or PF)	II	2017-002333-40	
		CIDP	II	NCT04280718, NCT04281472	
			I	NCT04073589, NCT03457649, NCT03334084	
Nipocalimab (M281; Momenta Pharmaceuticals)		WAIHA	III	NCT04119050	
		HDFN	II	NCT03842189, NCT03755128	(107, 108)
	pH 6.0: 0.04	MG	II	NCT03896295, NCT03772587	
			I	NCT02828046	
Aglycosylated IgG1 mAb	pH 7.4: 0.03				
IMVT-1401 (RVT-1401; Immunovant)	None available	MG	II	NCT03863080	(109)
		Graves' ophthalmopathy	II	NCT03922321, NCT03938545	
		WAIHA	II	NCT04253236	
mAb					

Compound/ manufacturer	K_D (nM)	Indication(s)	Phase	Study number	Citations
CSL730 / M230 (CSL Behring)					
Recombinant trivalent human IgG1 Fc multimer	None available		I	NCT03375606	
Orilanolimab (SYNT001/ ALXN1830; Alexion)		Pemphigus (PV or PF)	II	NCT03075904	(110, 111)
	pH 6.0: 1.19 pH 7.4: 0.87	WAIHA	II	NCT03075878, NCT04256148	
IgG4 mAb (S241P mutation)			I	NCT03643627	
ABY-039 (Alexion)			I	NCT03502954	
Bivalent antibody-mimetic	None available				

MG: Myasthenia gravis
ITP: Immune thrombocytopenia
PV/PF: Pemphigus vulgaris / Pemphigus foliaceus
CIDP: Chronic inflammatory demyelinating polyneuropathy
WAIHA: Warm autoimmune hemolytic anemia
HDFN: Hemolytic disease of fetus and newborn

Patel et al., *Clinical Reviews in allergy and immunology*, 2020

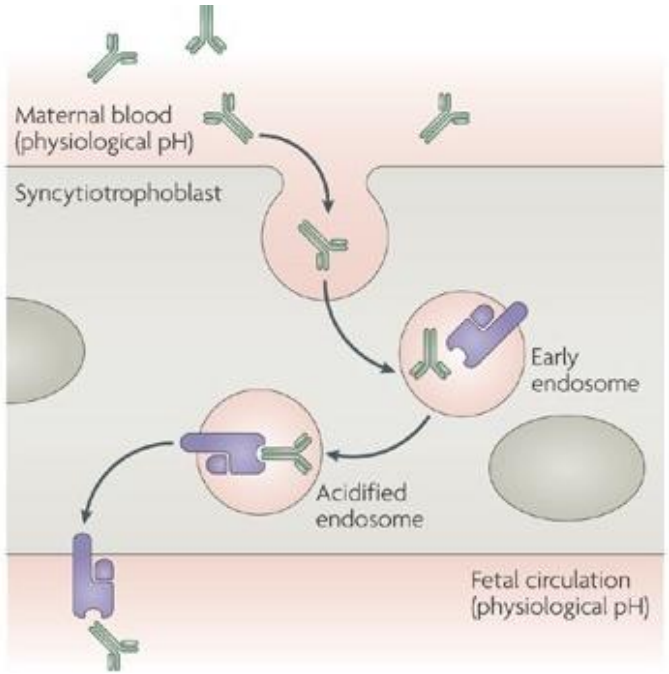
Biohaven Alternative to FcRn Inhibitor: The Hepatic Asialoglycoprotein (ASGPR) Receptor Degrader



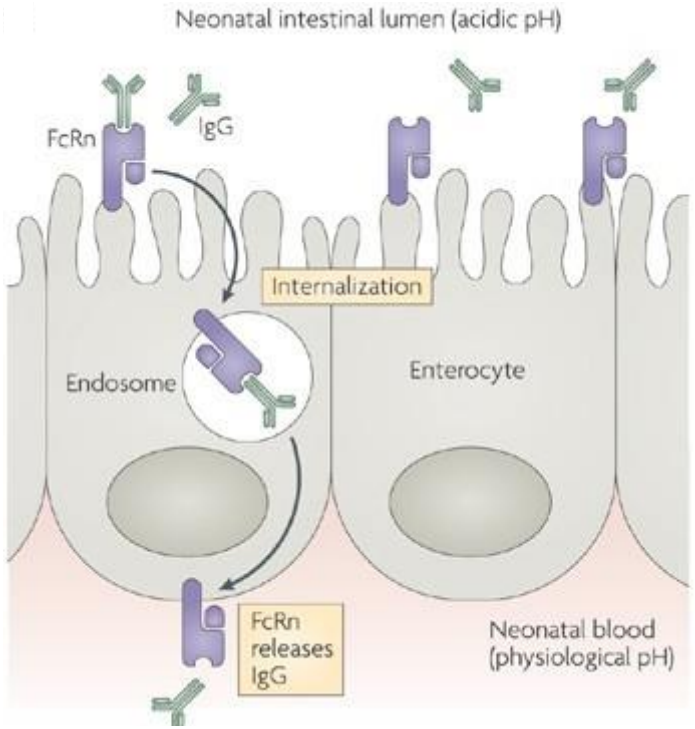
Sources: Biohaven Corporate Presentation, Sep 2023. Also see https://www.nature.com/articles/s41589-021-00851-1.

FcRn Plays Diverse Roles in Humoral Immunity that go Beyond Recycling IgG

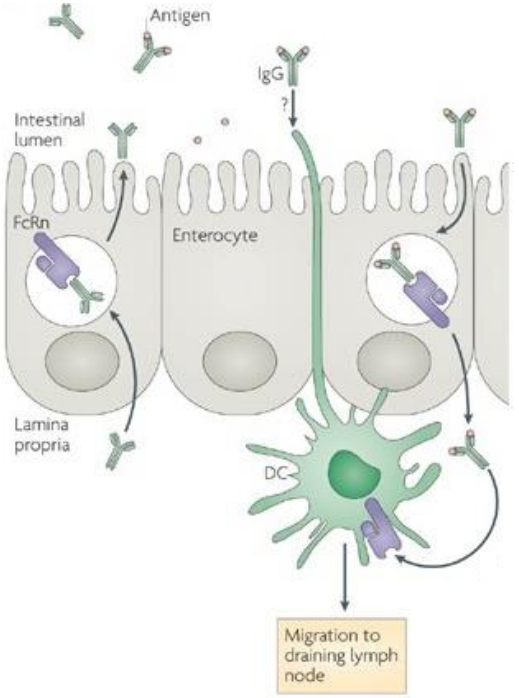
FcRn transports IgG from the maternal into the fetal circulation



FcRn transfers IgG from maternal milk across the intestinal wall in neonates



FcRn mediates trans-epithelial transfer of antigen bound IgGs, which then get taken up by DCs to prime adaptive immune responses



Roopenian et al., *Nature Reviews Immunology*, 2007

Future of Fc Gamma / FcRn Therapeutics

FcRn goes well beyond IgG recycling – has potential to be used in managing adaptive cellular autoimmunity.

FcRIIB has substantial value in autoimmunity and is the subject of at least two biotech start-ups.

FcRIIA also has substantial value in autoimmunity and is the subject of at least one biotech start-up.

There are a number of additional ligands of FcRn which have potential utility in managing IgG recycling.

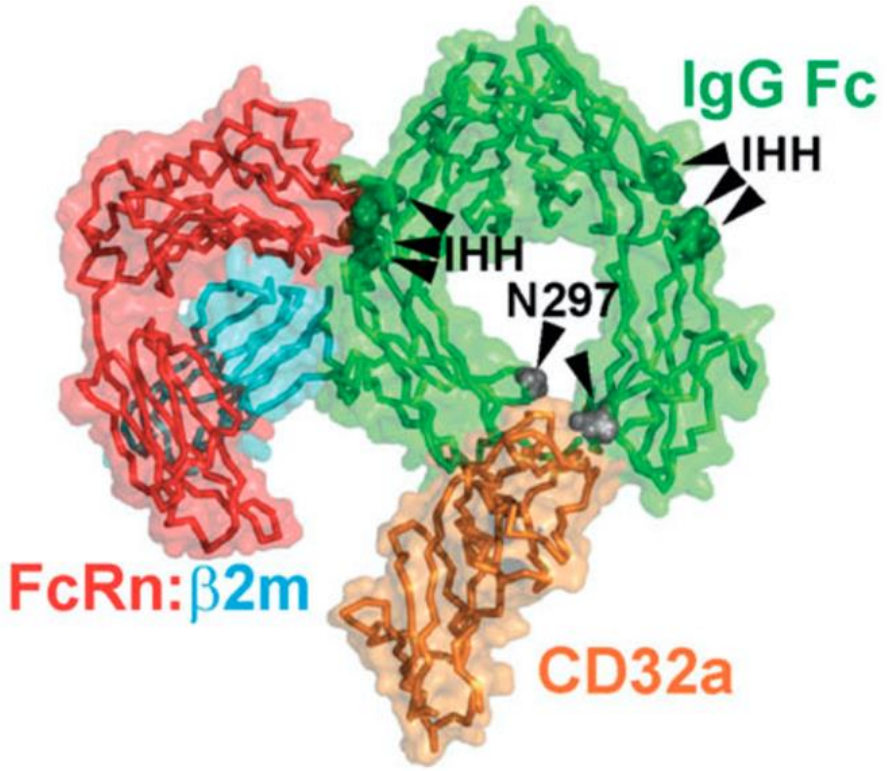
We are in early days of FcRn therapeutics. There are numerous emerging approaches in development to extend on the impressive results already obtained by first generation IgG transcytosis inhibitors that are in use today.

The Biology of CD32A and CD32B

- CD32A/B are low affinity receptors that only make stable interactions with IgG Immune Complexes (IC's)
- CD32A sends activation signals to the cell, whereas CD32B relays inhibitory ones
- It is widely accepted that classical FcγRs receptors such as these two mediate the effects of IgG IC's on the immune system
- CD32A polymorphisms are associated with disease susceptibility and protection
  - Individuals can carry either an arginine (R) or histidine (H) at amino acid position 131 in the CD32A protein
  - The 131H variant is common: it is estimated that 70% in Japanese and 50% in Caucasian individuals[1]
  - 131H binds IgG more tightly and is associated with ulcerative colitis[2,3,4] and resistance to anti-TNFa treatment for rheumatoid arthritis[5,6]
  - 131R has lower affinity for IgG subtypes and has been linked to infectious disease complications[7,8]

1. Osborne et al., *J Immunol Methods,* 1994; 2. Asano et al., *Nature Genetics*, 2009; 3. Jostins et al., *Nature*, 2012; 4. Anderson et al., *Nat Genetics*, 2011; 5. Davila-Fajardo et al., *Pharmacogenomics,* 2015; 6. Avila-Padretti et al., *PLOS ONE*, 2015; 7. Endeman et al., *Clin Vaccine Immunol*, 2009; 8. Li et al., *Curr Top Microbiol Immunol*, 2014

FcRn, IgG IC, and CD32A Form a Ternary Complex to Activate the Immune System



Immune activating ternary complexes:

- Richard Blumberg of the Brigham and Womens Hospital and colleagues have recently shown that IgG ICs simultaneously bind to FcRn and CD32A to form ternary complexes[1]
- The complexes have been detected using independent methods including protein co-immunoprecipitation, proximity ligation, and ELISA[1,2]
- Consistent with the critical role of FcRn and FcγRs for IC-mediated immune modulation, the formation of this complex is abolished if FcRn or the partner FcγR are not able to bind IgG[1,2]
- In all cases, the CD32a-131H variant, which binds IgG more tightly and is associated with autoimmune disease, increases ternary complex formation[1,2]

1. Hubbard et al., *J Exp Med*, 2020; 2. Cines et al., *Blood*, 2020

Start-Ups Focusing on FcγIIB Agonism

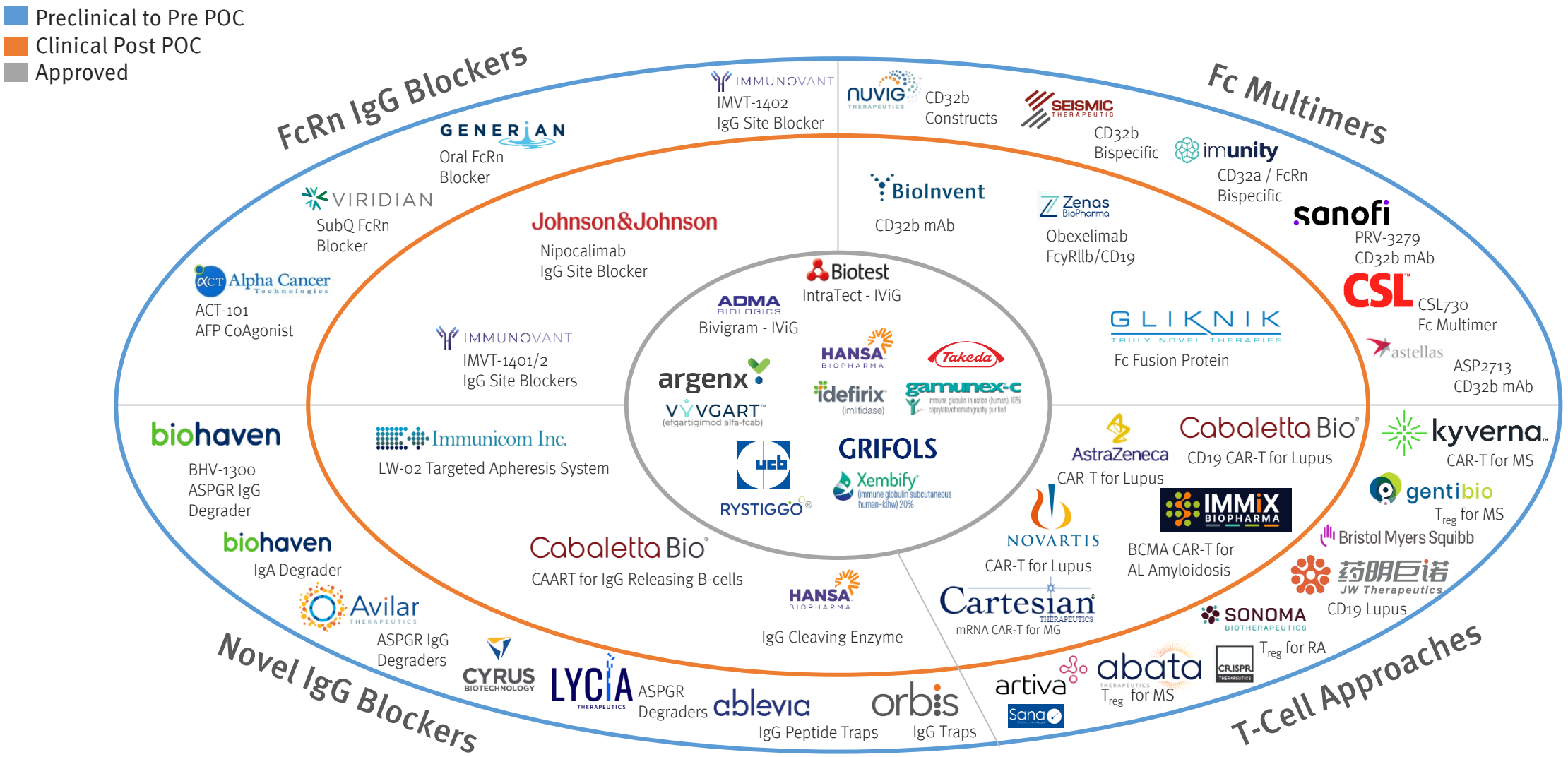
Website: https://www.nuvigtherapeutics.com/

Nuvig Therapeutics is a science-driven research and clinical development organization focused on translating novel scientific insights into therapies for patients with inflammatory and autoimmune diseases. We do not rely on traditional immune suppressive mechanisms but focus on the therapeutic induction of natural mechanisms of immune homeostasis to modulate immune function. Our pipeline will expand into a platform of products specifically targeting different autoimmune indications.

Website: https://seismictx.com/

Seismic's DcB antibody approach targets dysregulated cell-mediated immunity by optimally engaging both T cells and antigen presenting cells (APCs), such as B cells to restore homeostasis. Activating these pathways may control multiple diseases, such as multiple sclerosis, lupus and rheumatoid arthritis. The presentations demonstrate the application of IMPACT platform to identify and optimize novel antibody molecules that simultaneously engage multiple inhibitory pathways in more than one immune cell type, thereby targeting and regulating both sides of the immune synapse. Lead DcB antibody program which agonizes an inhibitory checkpoint receptor on T cells and selectively engages the inhibitory Fc receptor FcγRIIb on B cells/APCs to restore homeostasis in cell-mediated autoimmune diseases.

Pipeline of Drugs that Ablate Autoantibodies and B-Cells



Source: Stifel Research

Immunology: Complement System

Complement System Map

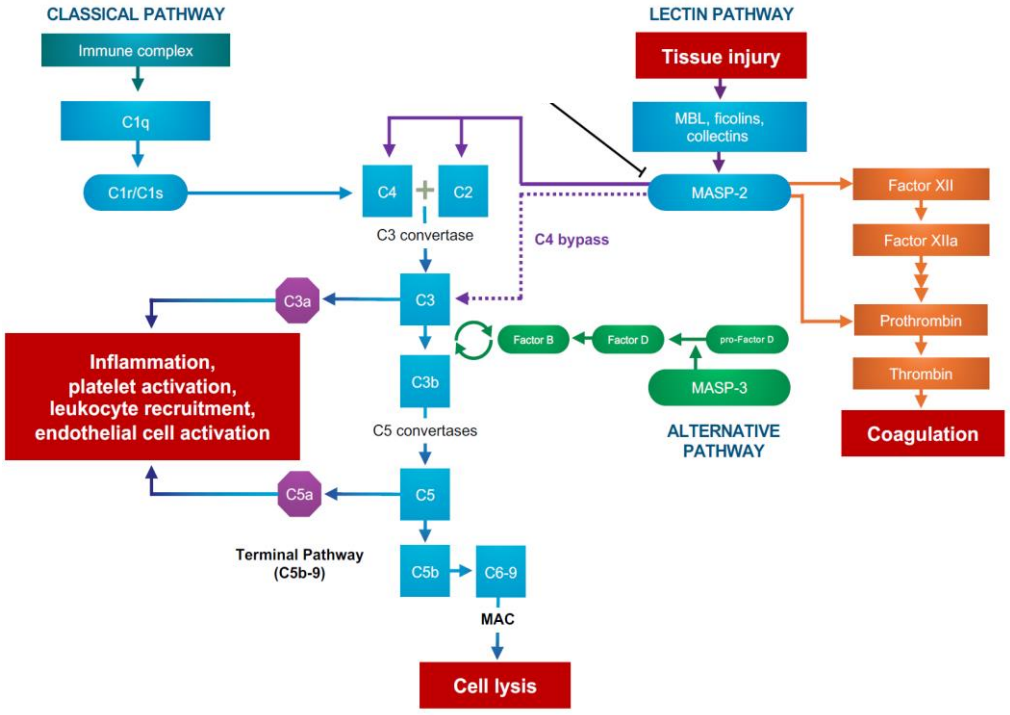
The complement system (CS) is one of the first lines of innate immune defense and plays an important role in the homeostasis of adaptive immunity response. In humans, it was identified as the heat-labile component of serum that assists, or *complements*, the action of antibodies which are in charge of killing bacteria.

In addition, the CS comprises more than 60 plasma and surface proteins. These are covered by nine central components of the cascade (C1 to C9), multiple activation products (such as C3a and C3b), regulators and inhibitors (e.g. Factor H and C4BP), proteases and newly assembled enzymes (e.g. C4b2a and Factor B), or effector molecule receptors (such as C3aR and C5aR)

Complement system proteins in the blood interact to recognize, opsonize, and clear or kill invading microorganisms, altered (unwanted) host cells, and other foreign materials. The complement system works together with the adaptive immune system but can also serve as an alternative to the classic adaptive immune system.

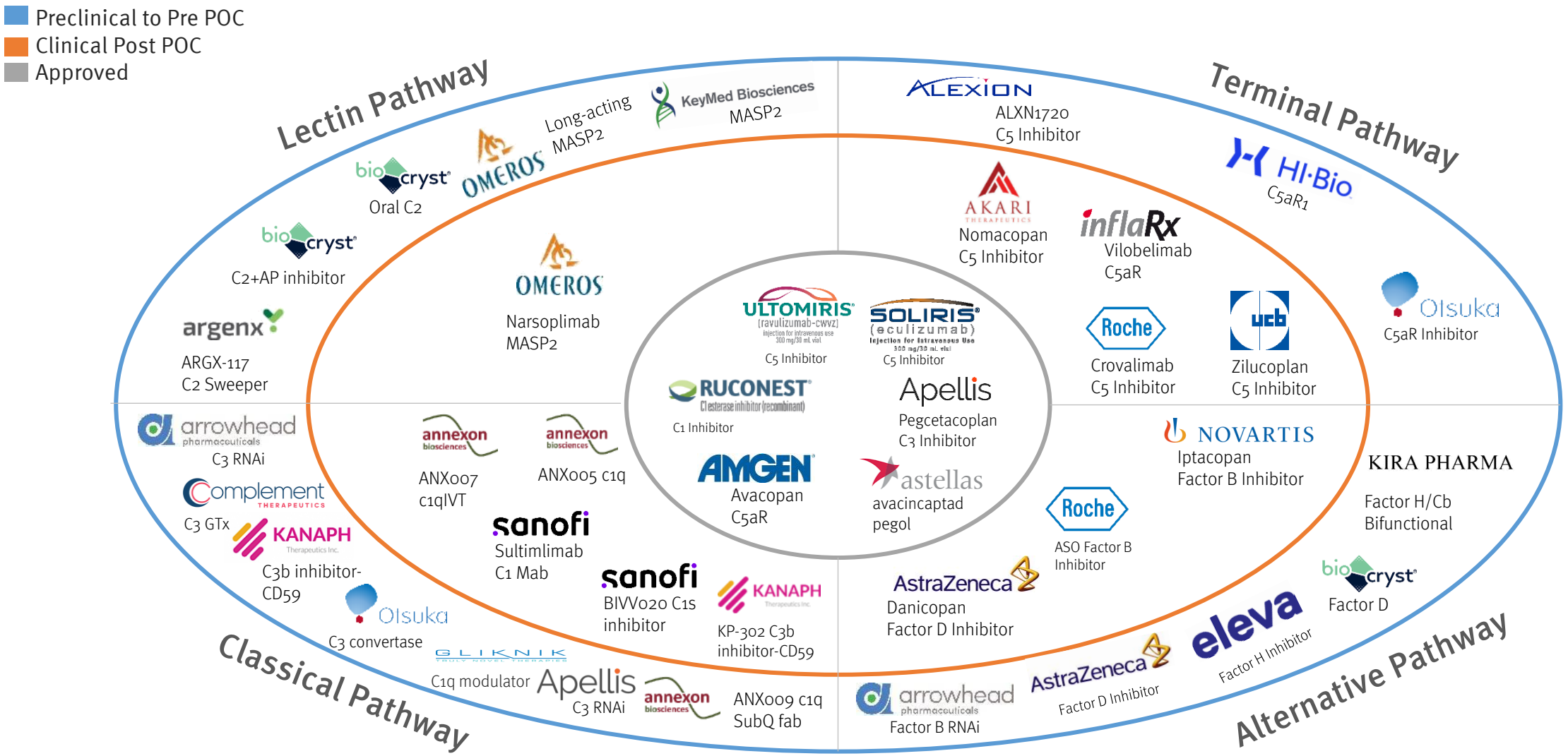
There are three pathways of complement activation: the classical pathway, which is triggered directly by pathogen or indirectly by antibody binding to the pathogen surface; the MB-lectin pathway; and the alternative pathway, which also provides an amplification loop for the other two pathways.

The complement system impacts the adaptive immune system (e.g., inflammation, leukocyte recruitment) via the Classical C3a and C5A pathways. The complement system impacts coagulation via the Lectin Pathway. The main effect of C5 activation via the Terminal Pathway is the production of Membrane Attack Complex (MAC) which leads to cell lysis and destruction.



Source of graphic: OMEROS Investor Presentation

Pipeline of Drugs that Operate Through Complement System



Source: Stifel Research

Immunology: Innate Immune System and Inflammation: Macrophages and Neutrophils

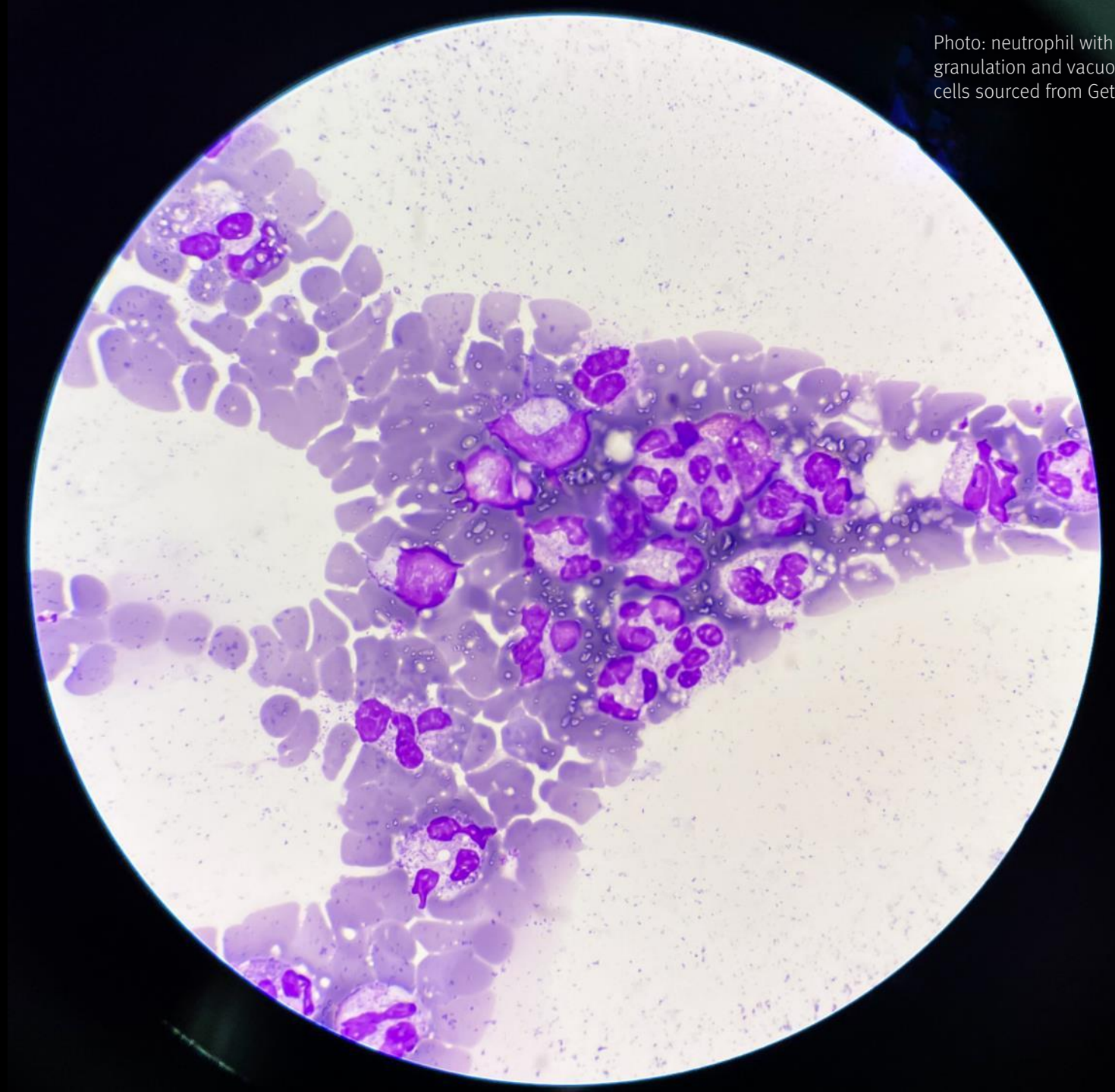
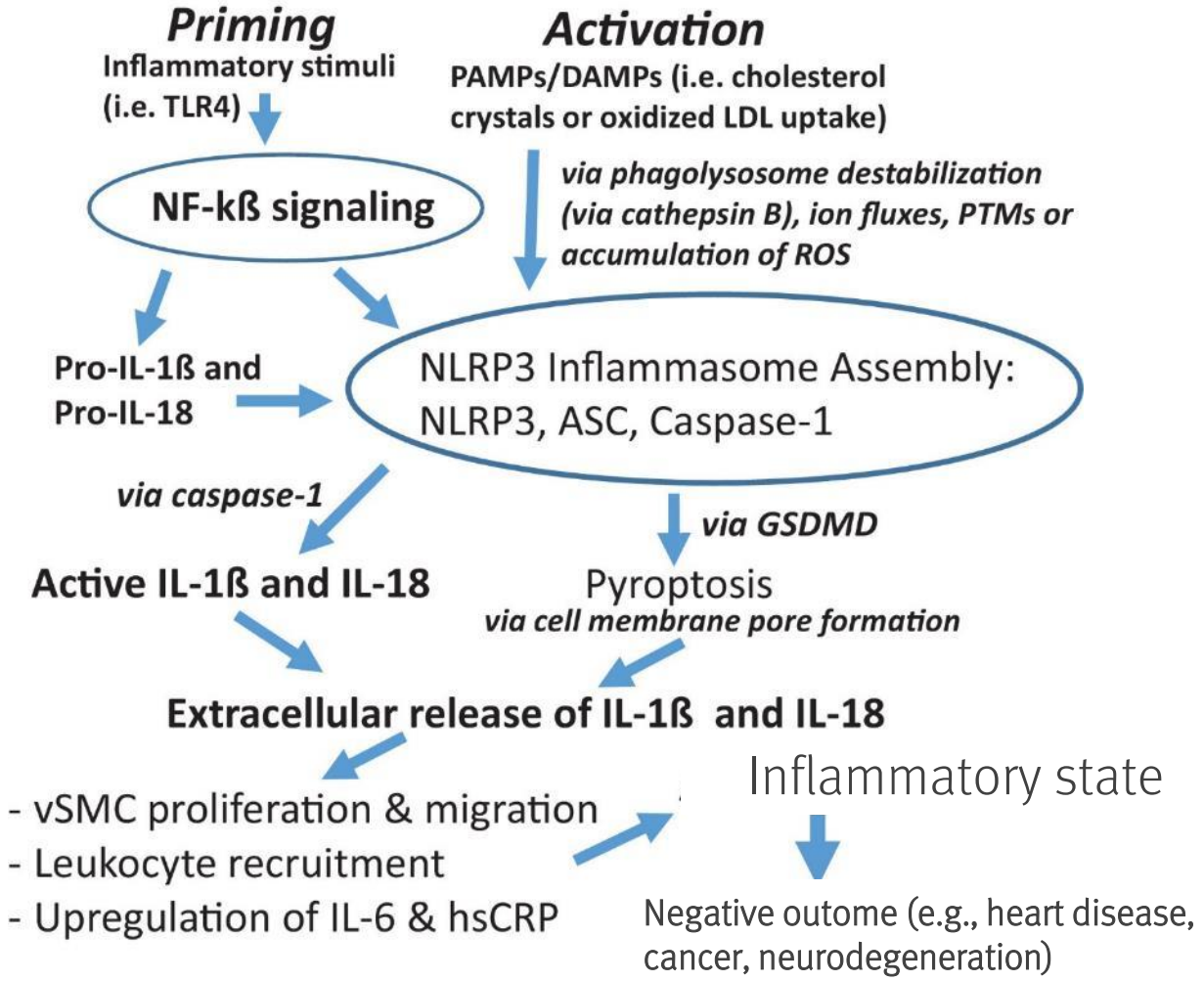


Photo: neutrophil with toxic granulation and vacuole inflammatory cells sourced from Getty Images.

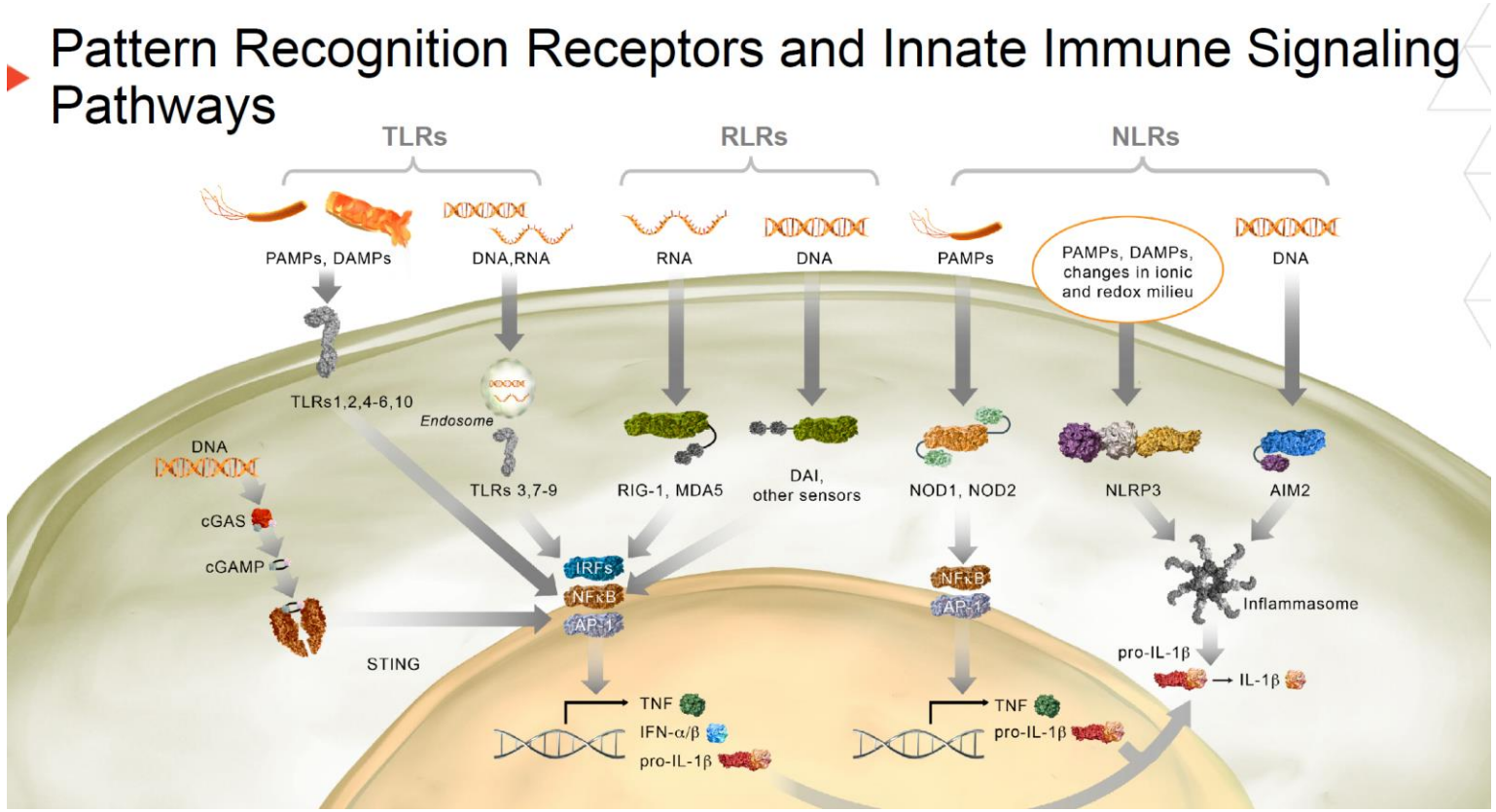
Innate Immune System Biology: IL-1 Pathway



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.

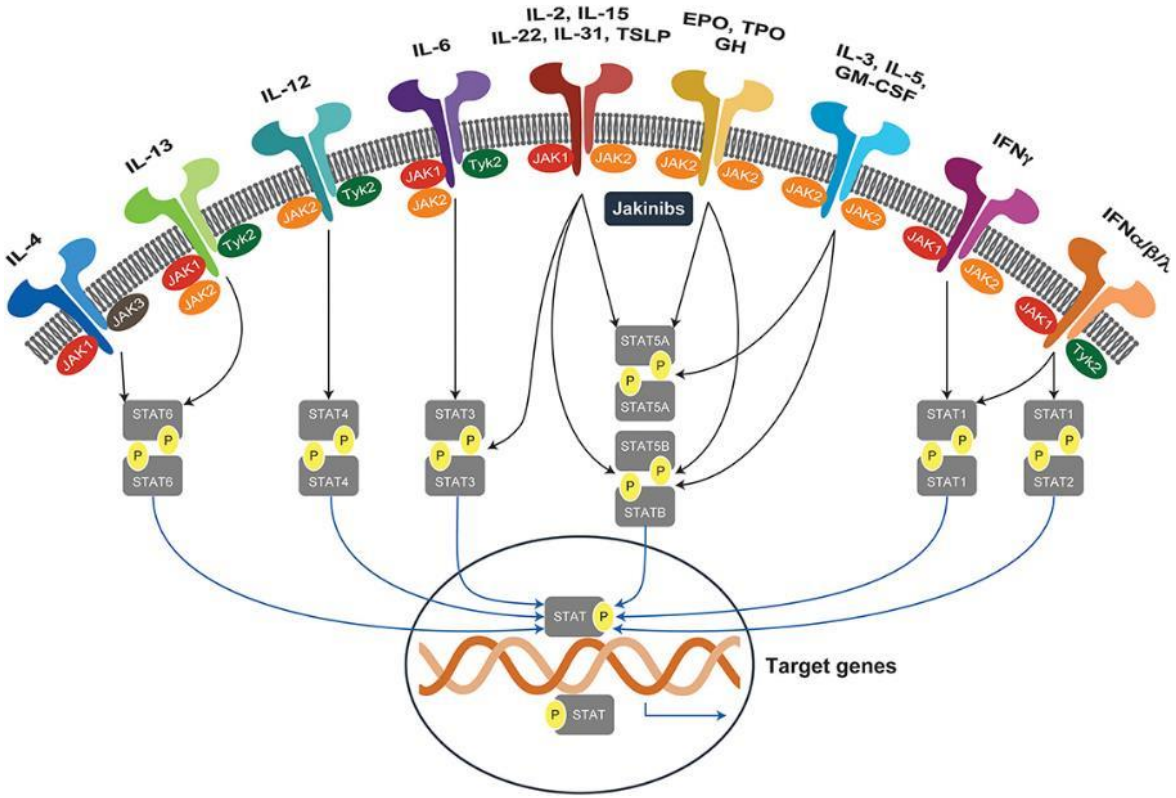
Source: https://www.translationalres.com/article/S1931-5244(19)30166-5/fulltext

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

JAK/STAT Pathway Receives Signals from External Cytokines (e.g., IL-6) and Triggers STAT Transcription of Key Gene Products



- Some of the downstream products of the IL-1 pathway can also activate the JAK/STAT pathway.
- This pathway ultimately leads to transcription of pro-inflammatory gene products and cytokines.
- Its activities on STAT proteins (STAT1 through STAT8) are controlled by JAK1, JAK2, JAK3 and TYK2.
- Pharmaceutical modulation of the JAK and STAT pathways has been productive in diseases such as IBD, RA, atopic dermatitis and GVHD.

Innate Immune Biology Dendrogram: Macrophages and Neutrophils

Top Approved Drugs in this Field

α4β7: Entyvio vedolizumab

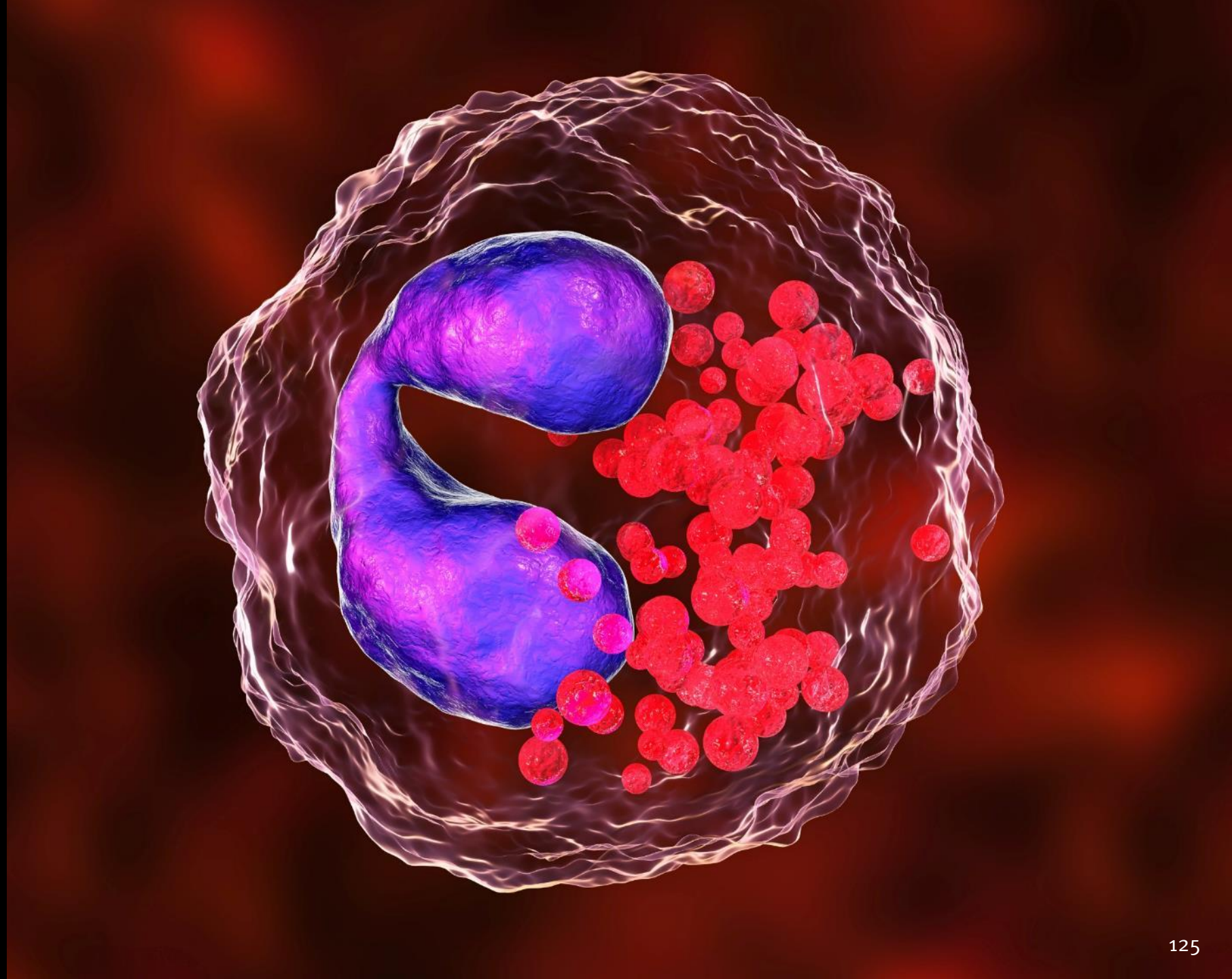
IL-1: Arcalyst (rilonacept) injection for Subcutaneous Use; ILARIS (canakinumab); Kineret (anakinra)

IL-6: ACTEMRA tocilizumab; ENSPRYNG satralizumab-mwge subcutaneous injection 120 mg/mL; KEVZARA (sarilumab); sylvant siltuximab

JAK: Jakafi ruxolitinib (tablets); olumiant (Baricitinib) Tabletten; RINVOQ upadacitinib 15mg tablets; XELJANZ [tofacitinib]

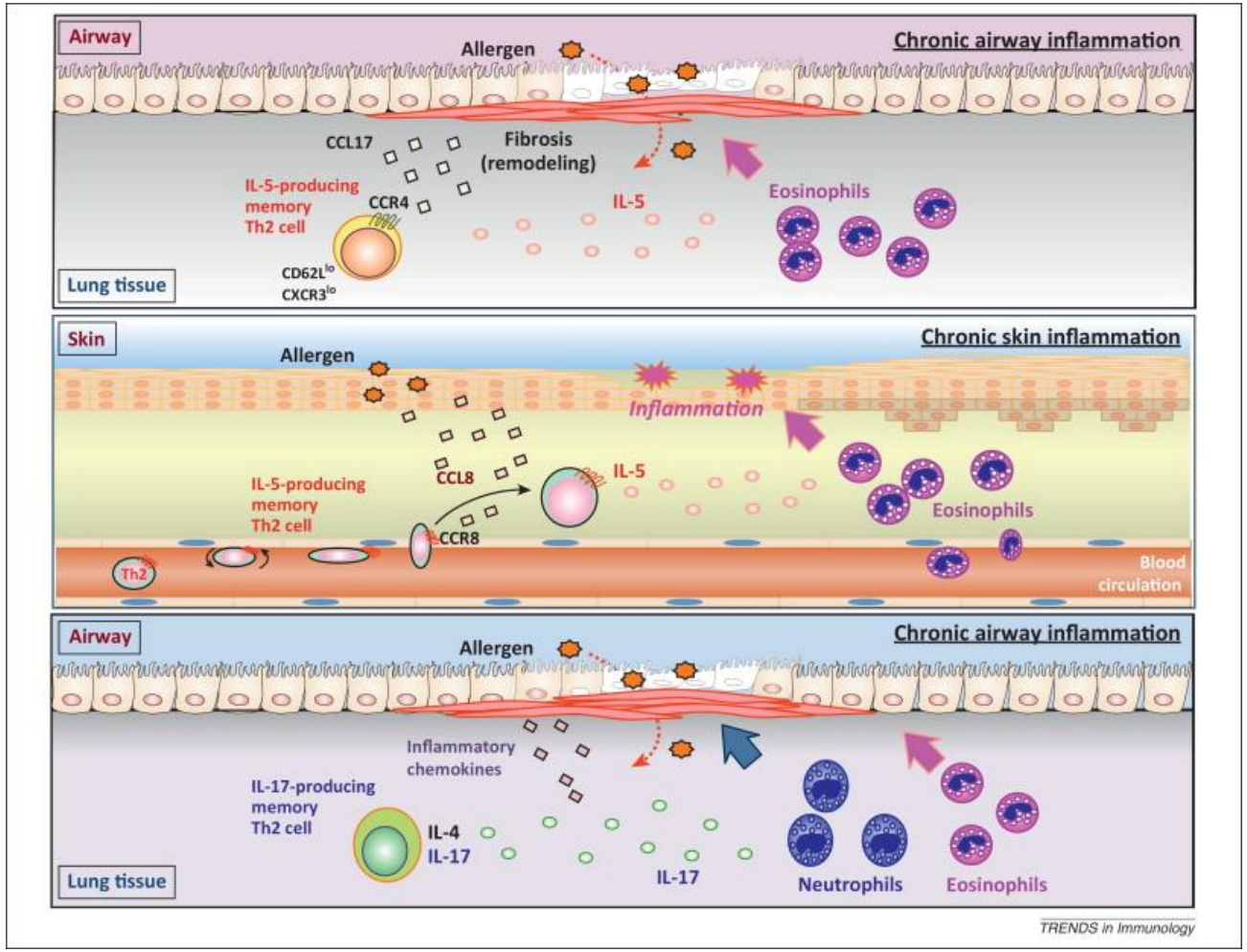
Source: Stifel research and analysis

Immunology:
Innate Immune System and Inflammation: Eosinophils & Mast Cells



Eosinophils Behind Many Autoimmune Airway and Skin Diseases

Immunopathology of asthma and atopic dermatitis involves excess activity of eosinophils.



Asthma

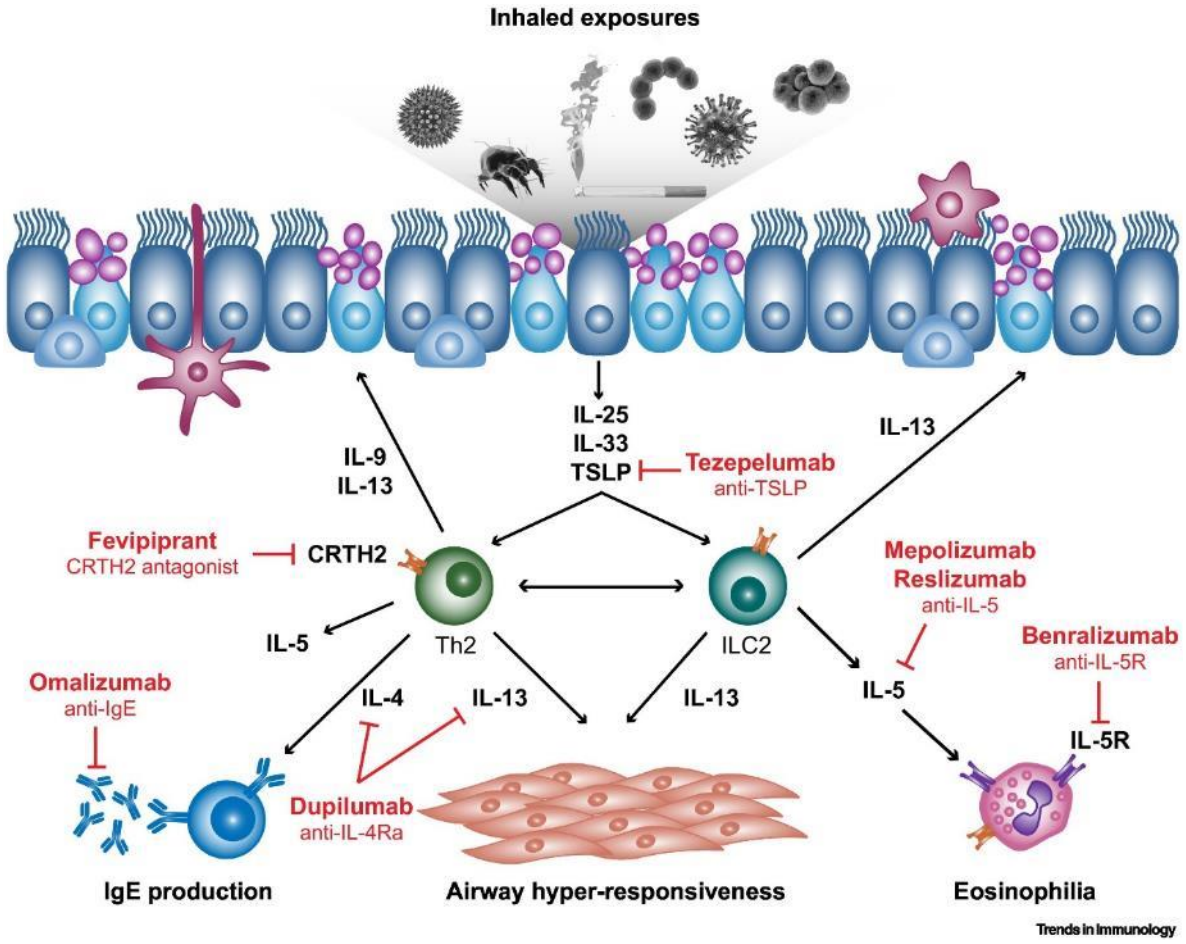
Atopic Dermatitis

Severe Asthma / COPD

Source: Endo Y, Hirahara K, Yagi R, Tumes DJ, Nakayama T. Pathogenic memory type Th2 cells in allergic inflammation. *Trends Immunol.* 2014 Feb;35(2):69-78.

Eosinophil / IgE Biology: Type 2 Immune Responses

Drivers of Childhood Asthma (airway hyper responsiveness)



Type 2 immune responses involve induced following exposure, for example, to allergens, and are characterized by the production of IL-4, IL-5, and IL-13. They play a critical role in the pathophysiology of allergic diseases such as asthma and allergic rhinitis. Type 2 responses are also critical against helminths invading cutaneous or mucosal sites.

Type 2 innate lymphoid cells (ILC2s) cells of lymphoid origin, derived from common lymphoid progenitors; defined by the absence of antigen specific B or T cell receptor due to a lack of recombination activating gene (RAG). ILC2s express the GATA3 transcription factor, are commonly involved in type 2 immune responses, and secrete type 2 immune mediators, such as IL-4, IL-5, and IL-13.

Source: Lloyd CM, Saglani S, 2019, Opening the Window of Immune Opportunity: Treating Childhood Asthma, *Trends in Immunology*, Vol: 40, Pages: 786-798

Innate Immune Biology Dendrogram: Eosinophils / Mast Cells

CRTH2	DP2	Eotaxin-1	Galectin-10	IgE
IL-4a / IL-13	IL-5	IL-9	IL-13	IL-25
IL-31	IL-33	PI3Kδ	Siglec-8	TSLP

Source: Stifel analysis

Disclosure

STIFEL | Healthcare

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