South San Francisco Skyline

Biopharmaceutical Sector

Weekly Update – October 2, 2023

STIFEL | Healthcare

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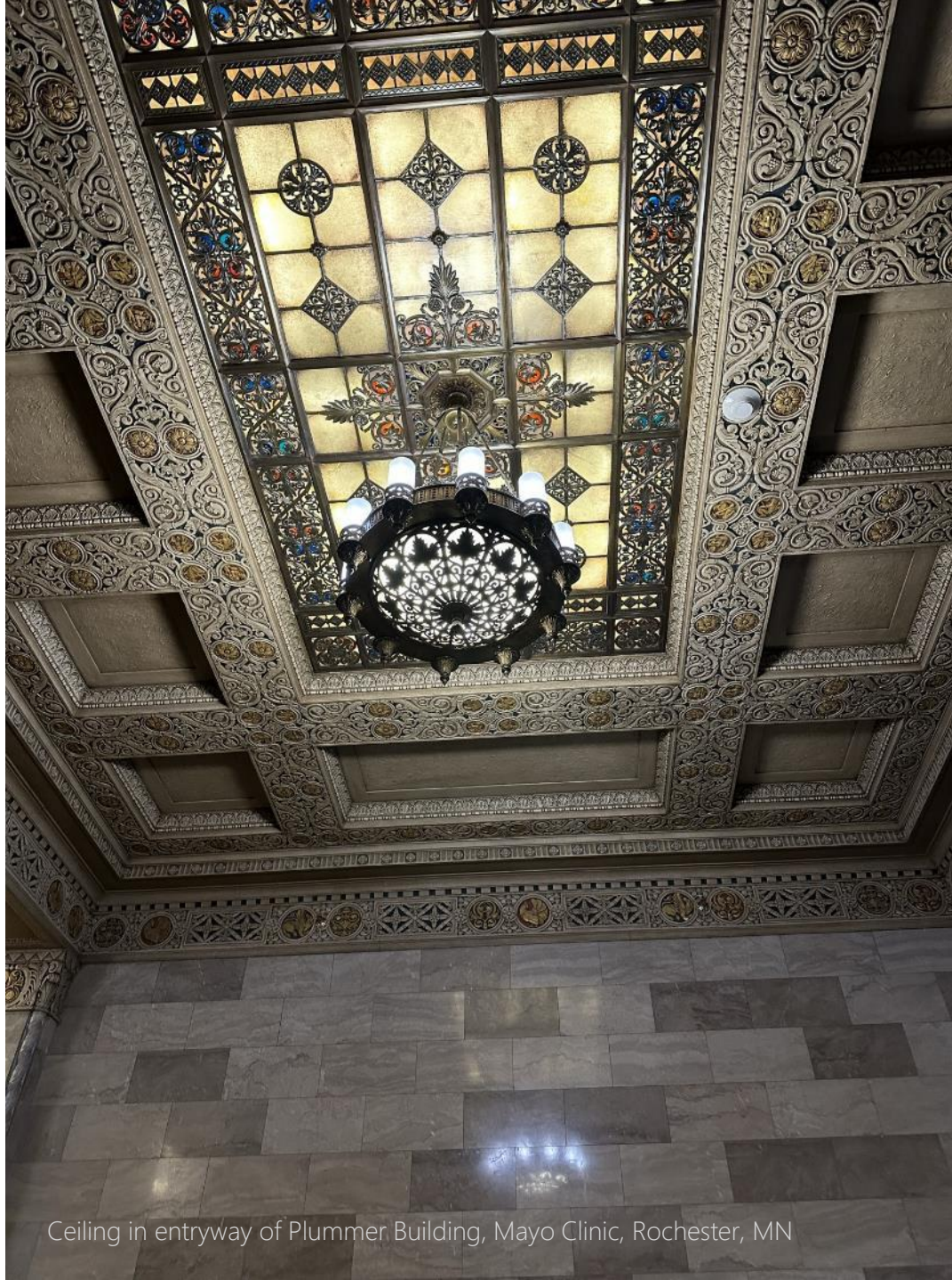


Ceiling in entryway of Plummer Building, Mayo Clinic, Rochester, MN

Strong Partner in a Turbulent Environment

The biopharma industry environment is facing unprecedented challenges amidst a turbulent global economic and geopolitical environment.

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

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

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

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

STIFEL | Healthcare

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

Past Issues / Mailing List

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

Recent issues in case you missed and want to read:
September 25, 2023 (Target ID)
September 18, 2023 (Changing Pharma Strategy)
September 11, 2023 (US Health System)
September 5, 2023 (FTC, IRA, Depression)
August 21, 2023 (Covid, China)
August 7, 2023 (Employment, Summer reading)
July 24, 2023 (Alzheimer's Disease)
July 7, 2023 (Biotech market review – H1 '23)
July 1, 2023 (Obesity drugs)
June 19, 2023 (Generative AI)
June 12, 2023 (IRA, State of Industry)
May 29, 2023 (Oncology update)
May 22, 2023 (FTC case on Amgen/Horizon)

Science geeks united.

Join Us at These Upcoming Events

1

Biotech Hangout held its latest event on September 29th.

The next event will be on October 6, 2023.

Please join us.

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

2

biofuture™

New York City | October 4-6, 2023

Innovators & Investors Come Together to Shape the Future of Healthcare

At this year's summit, BioFuture attendees will be exploring the exciting mashup between rapidly evolving fields including biopharma, digital medicine, big data, AI, healthcare systems, payors, and more. The coming decade will dramatically accelerate the transformation of the healthcare ecosystem. Be part of the discussions that will shape and transform the future of healthcare.

To Learn More
https://biofuture.com/

3

BIO-EUROPE®

Munich | Nov 6-8, 2023

BIO-Europe convenes over 5,500 attendees, representing 60 countries and 2,220+ companies, making the event the industry's largest gathering of biopharma professionals in Europe.

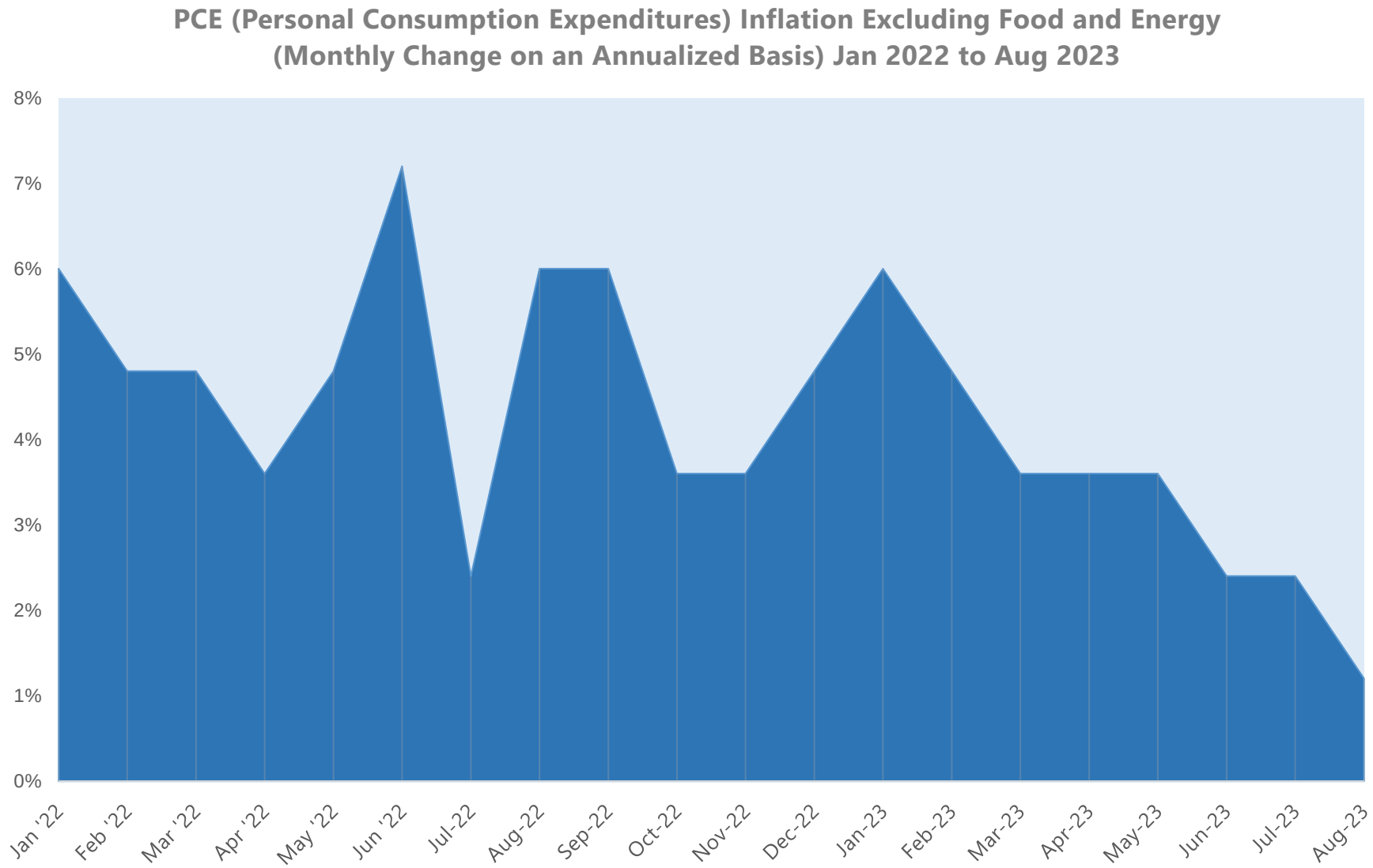
To Learn More
https://informaconnect.com/bioeurope/

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

Macro Update

Entry to Plummer Building Mayo Clinic, Rochester, MN

U.S. PCE Inflation in August Improved Materially



The Fed's preferred inflation gauge is PCE inflation. Energy and food prices are volatile.

If one excludes food and energy prices, PCE Inflation fell to 1.2% in August (on a month-to-month basis).

The trend looks good and could portend an improving biotech market if the trend continues.

Source: Bureau of Economic Analysis, Department of Commerce.

The Fed's Favorite Inflation Indicator Rose Less Than Expected in August

Jeff Cox, *CNBC*, Sep 29, 2023

An economic indicator the Federal Reserve favors as an inflation gauge rose less than expected in August, showing that the central bank's fight against higher prices is making progress

The personal consumption expenditures price index excluding food and energy increased 0.1% for the month, lower than the expected 0.2% gain from the Dow Jones consensus of economists, the Commerce Department reported Friday. On a 12-month basis, the annual increase for core PCE was 3.9%, matching the forecast.

That was the smallest monthly increase since November 2020.

Along with the modest inflation gain, consumer spending rose 0.4% on a current-dollar basis. That was down sharply from 0.9% in July. In real terms, spending was up just 0.1% after rising 0.6% in July.

Including food and energy, headline PCE increased 0.4% on the month and 3.5% from a year ago. Headline inflation has been creeping higher in recent months after hitting 3.2% in June.

Core PCE inflation in the US is dropping fast.

This could be a major positive for stocks and biotech.

Source: https://www.cnbc.com/2023/09/29/pce-inflation-august-2023-good-news-for-inflation-hawks.html

House Passes Bill That Averts Government Shutdown

Wall Street Journal, Sep 30, 2023 (excerpt)

WASHINGTON—The House passed a measure to extend government funding through mid-November after a coalition of Republicans and Democrats joined ranks to stave off a government shutdown, putting the matter squarely in the hands of the U.S. Senate, which is expected to also pass the bill.

The surprise progress upended expectations that Congress was too divided to pass anything in time to keep the government funded past 12:01 a.m. Sunday.

To become law, the legislation must also clear the Senate and be signed into law by President Biden. White House officials said Biden supports the measure.

The House voted 335-91 for the measure, which includes $16 billion in disaster relief but omits aid for Ukraine. That exceeded the two-thirds majority needed to clear the bill through the House, which considered the legislation under special procedures requiring a supermajority of votes. All but one Democrat voted in favor of the measure, while nearly half of Republicans voted against it.

THE WHITE HOUSE
WASHINGTON

FOR IMMEDIATE RELEASE
September 30, 2023

On Saturday, September 30, 2023, the President signed into law:

H.R. 5860, which provides fiscal year appropriations to Federal agencies through November 17, 2023, for continuing projects of the Federal Government and extends several expiring authorities.

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Source: https://www.wsj.com/politics/policy/federal-government-shutdown-deadline-d714a1ef

Biopharma Market Update

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

Biotech Stocks Flat Last Week

The XBI was unchanged last week despite positive inflation news. Interest rates continued to rise.

Biotech Stocks Down Last Week

Return: Sep 23 to Sep 29, 2023

Nasdaq Biotech Index: 0.0%
Arca XBI ETF: 0.0%
Stifel Global Biotech (EV): +1.5%*
S&P 500: -0.7%

Return: Jan 1 to Sep 29, 2023

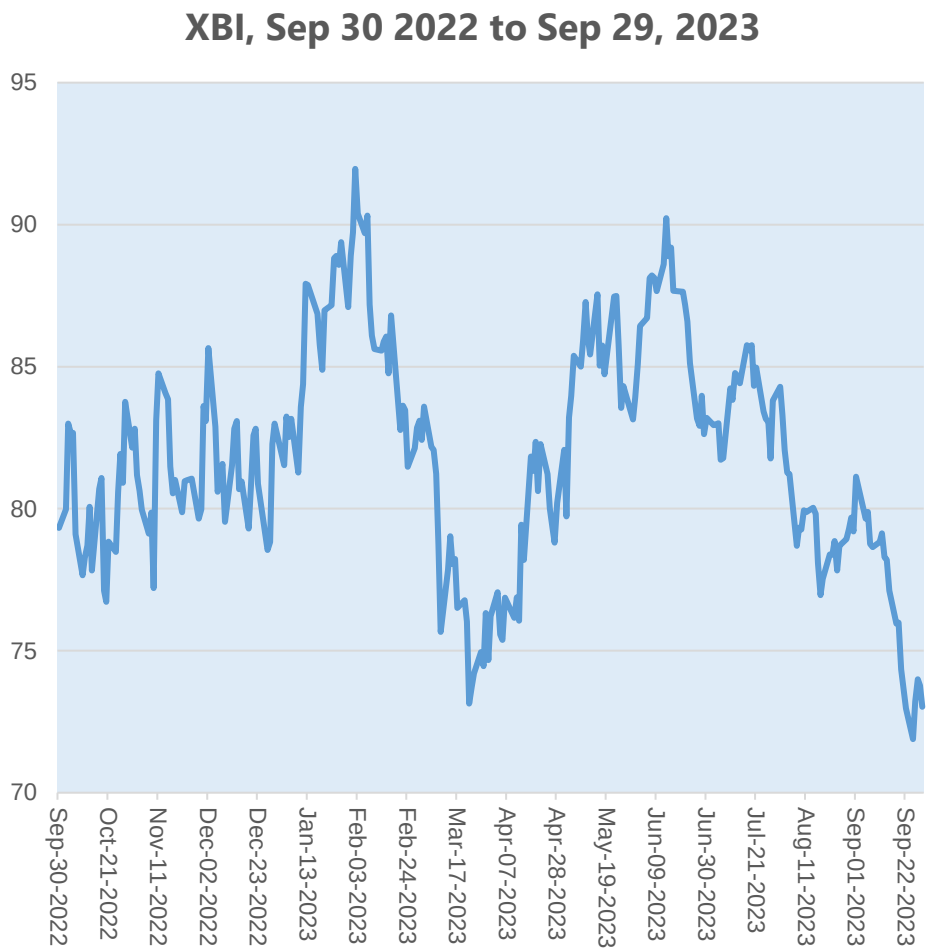
Nasdaq Biotech Index: -6.2%
Arca XBI ETF: -12.0%
Stifel Global Biotech: -13.6%*
Stifel Global Biotech (adjusted): -7.6%*
S&P 500: +11.7%

VIX Flat

Oct 21: 29.7%
Jan 20: 19.9%
Mar 17: 24.6%
May 26: 18.0%
July 21: 13.6%
Sep 8: 13.8%
Sep 23: 17.2%
Sep 29: 17.3%

10-Year Treasury Yield Up

Oct 21: 4.2%
Jan 20: 3.48%
Mar 17: 3.39%
May 26: 3.8%
July 21: 3.84%
Sep 8: 4.26%
Sep 23: 4.44%
Sep 30: 4.59%

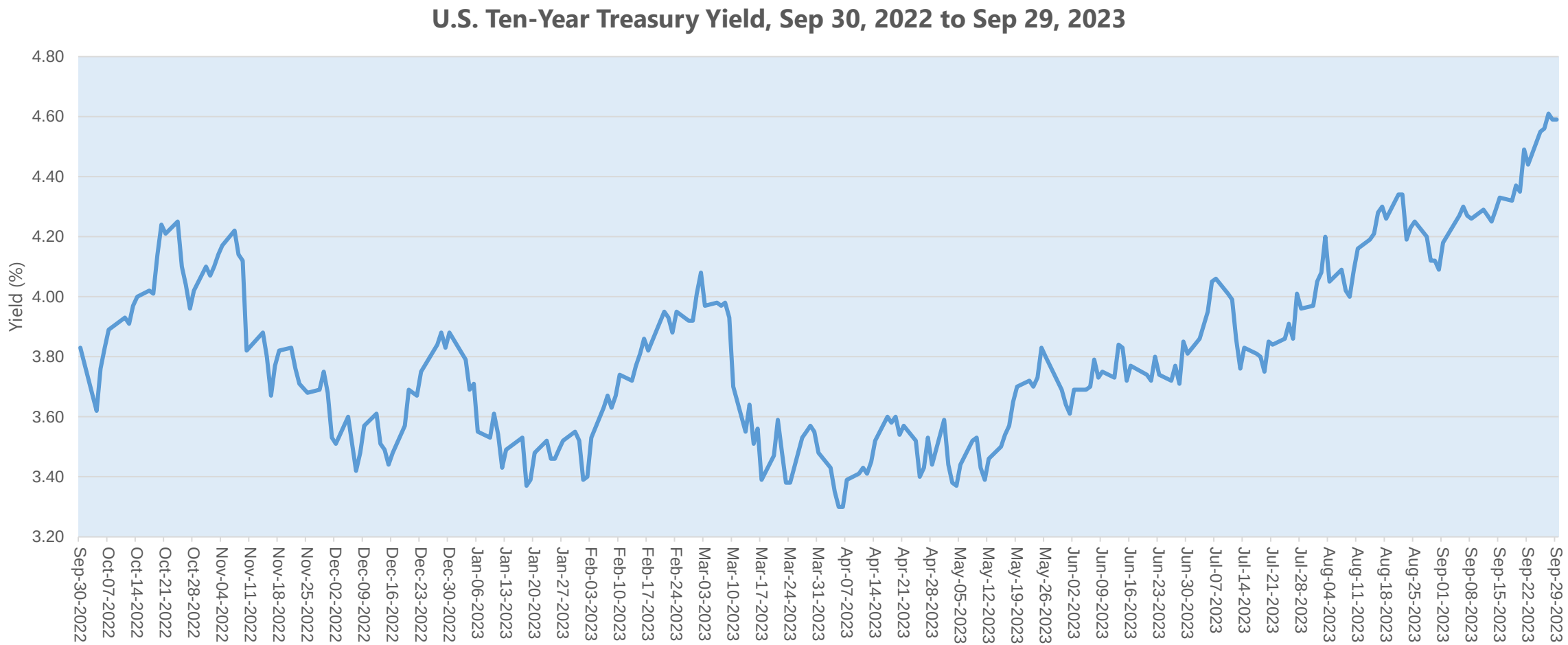


* Change by enterprise value. The adjusted number accounts for the effect of exits and additions via M&A, bankruptcies and IPOs.

Source: S&P Capital IQ and Stifel analysis

U.S. Long Bond Yields Continued to Rise Last Week

U.S. rates rose by 15 basis points last week as hedge funds piled onto the short trade. This is negative for biotech.

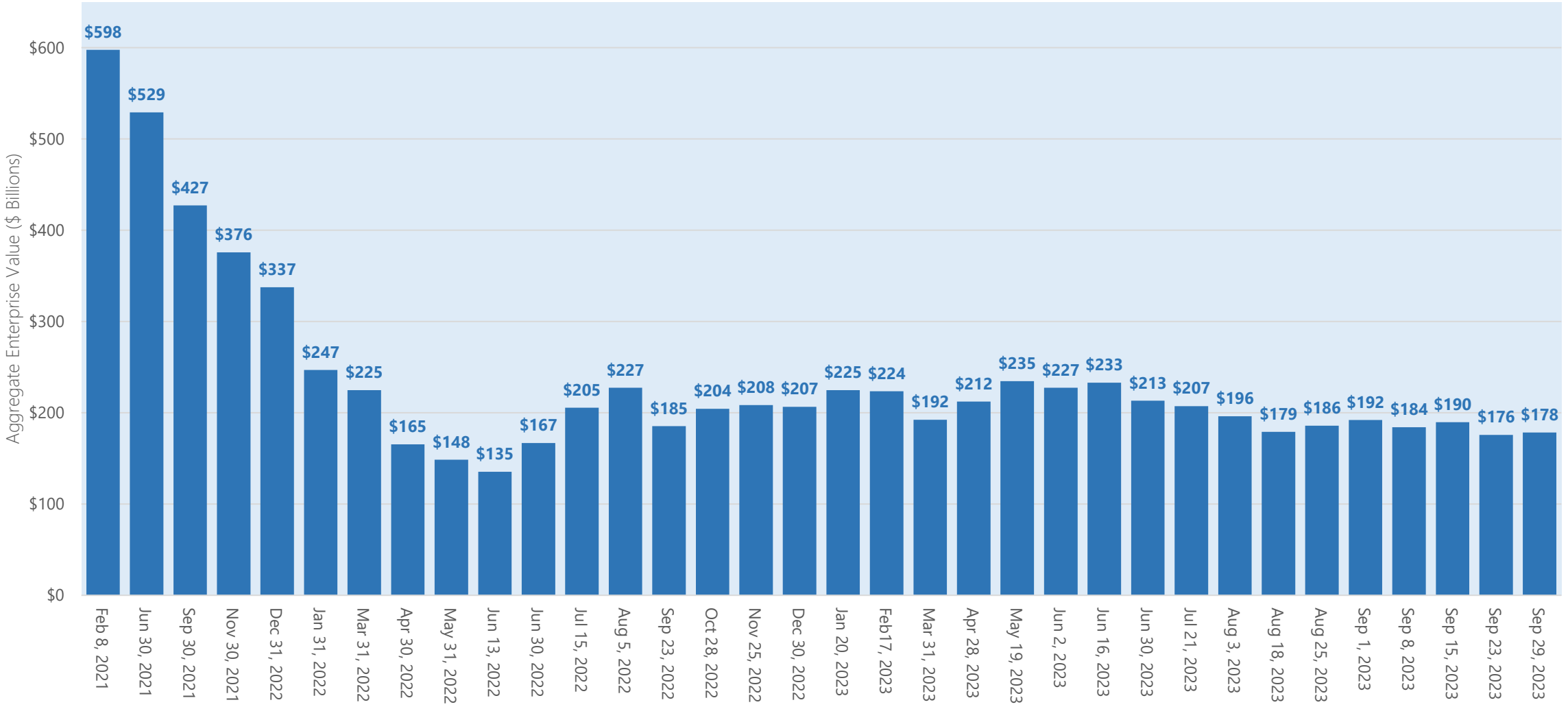


Source: CapitalIQ

Total Global Biotech Sector Value Up Slightly Last Week

The total value of the global biotech sector rose 1.5% last week, mainly on the heels of strong Immunovant performance.

Total Enterprise Value of Publicly Traded Global Biotech, Feb 8, 2021 to Sep 29, 2023 ($ Billions)



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

The Hedge Fund Winners From Immunovant's Rise

Stephen Taub, *Institutional Investor*, Sep 28, 2023

On Tuesday, Immunovant reported encouraging data from a Phase 1 clinical trial for an autoimmune treatment.

Its stock surged more than 97 percent on the news.

One of the biggest beneficiaries was Deep Track Capital, which owned 4.15 percent of the shares at the end of the second quarter. It is the life sciences hedge fund firm's sixth-largest long position.

Deep Track was formed in 2020 by David Kroin, who has spent more than 23 years investing in health care companies. Back in 2003, he co-founded Great Point Partners and was the co–portfolio manager for its equity long-short biotechnology hedge fund, as well as an investment committee member for its private equity funds investing in recaps and buyouts of health care companies.

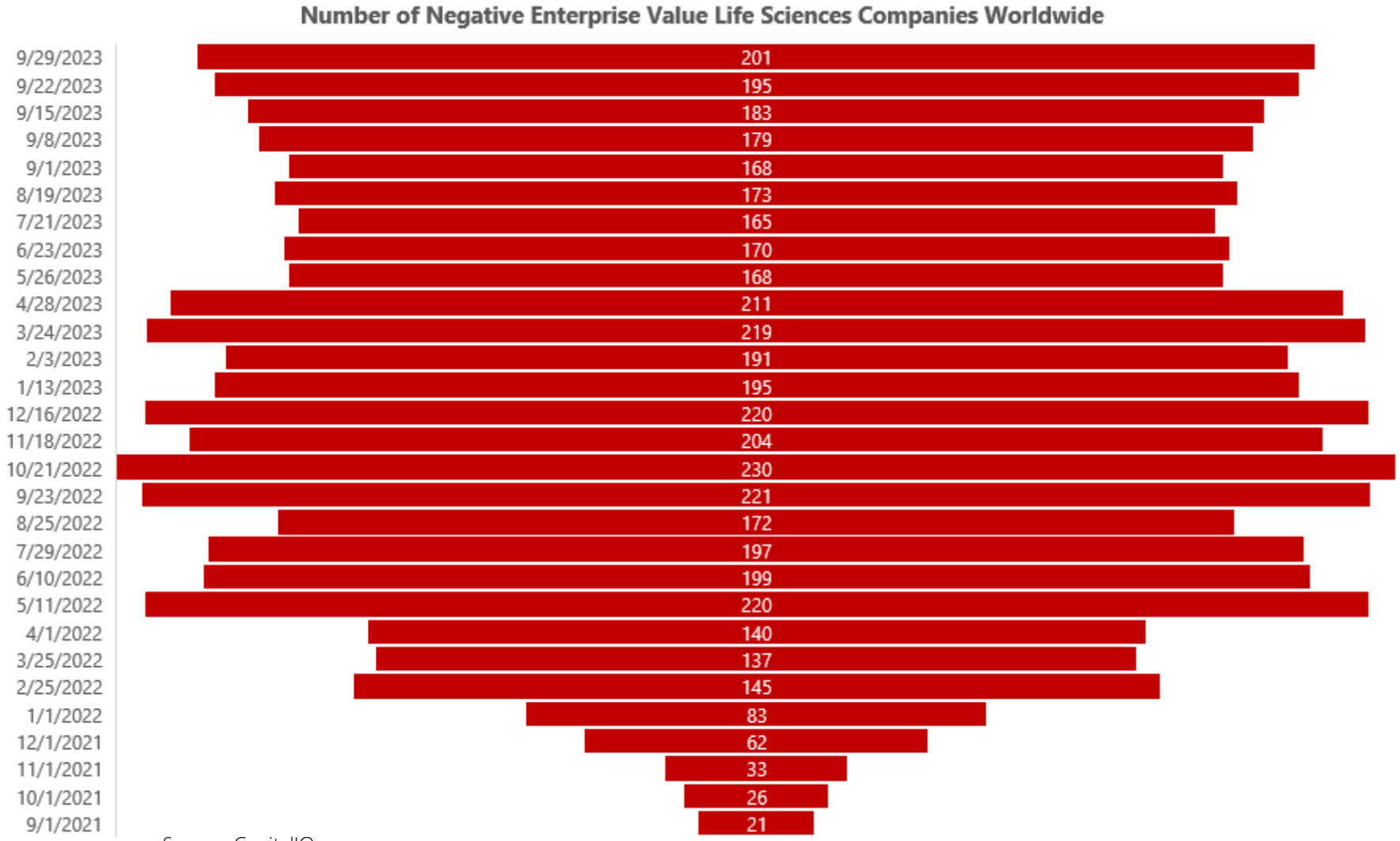
Through August, Deep Track was up between 8 and 9 percent for the year, according to a person who has seen the results.

At the end of 2022, the firm had about $3.7 billion in regulatory assets under management, according to a regulatory filing.

Hedge funds with smaller stakes in Immunovant include Perceptive Advisors, Avidity Partners Management, Redmile Group, and Cormorant Asset Management, among others.

Source: https://www.institutionalinvestor.com/article/2c90rlnzbsj6jm2s4dxq8/premium/the-hedge-fund-winners-from-immunovants-rise

Number of Negative Enterprise Value Life Sciences Companies Rose to 201 in Last Week



Source: CapitalIQ

The count of negative EV life sciences companies worldwide rose from 195 a week ago to 201 last Friday.

Public Life Sciences Sector Value Fell Last Week

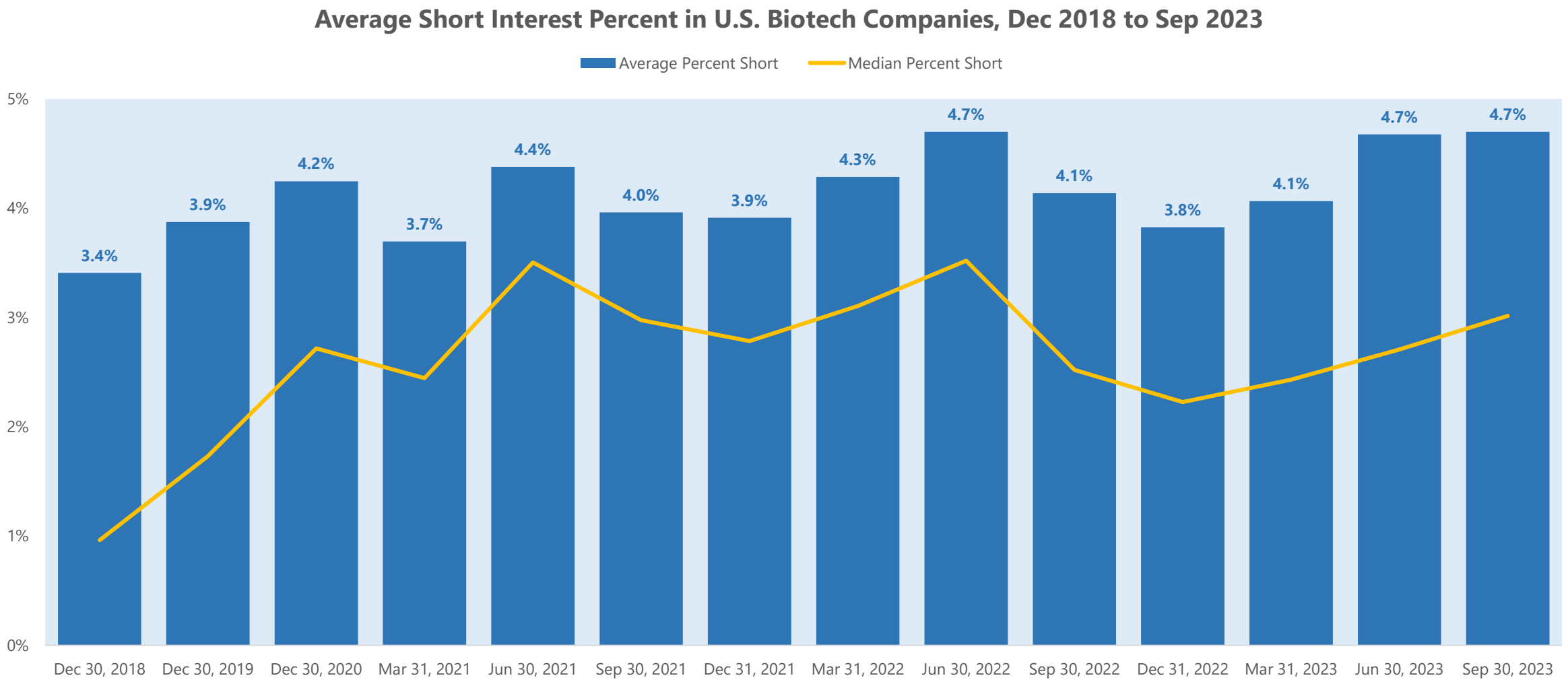
The total enterprise value of the publicly traded life sciences sector fell by 0.5% last week ($42 billion). The sectors that dropped the most were medical devices, OTC and commercial pharma. The top eight pharma have given up $100bn in value in the last two weeks.

Sector	Firm Count	Enterprise Value (Sep 29, 2023, $millions)	Change in Last Week (percent)	Change in Last Month (percent)	Change in Last Year (percent)
API	81	$81,024	2.0%	2.3%	-0.5%
Biotech	818	$178,457	-0.5%	-6.4%	-5.1%
CDMO	40	$156,318	0.0%	-7.6%	-8.0%
Diagnostics	83	$234,118	1.5%	-7.9%	11.6%
OTC	32	$29,595	-0.7%	-3.0%	8.1%
Commercial Pharma	723	$5,744,755	-0.6%	-2.3%	11.6%
Pharma Services	40	$199,914	1.3%	-4.7%	12.9%
Tools	54	$669,971	0.3%	-7.5%	-4.4%
Devices	181	$1,512,523	-1.1%	-6.1%	5.8%
HCIT	11	$22,833	3.2%	-4.4%	-3.8%
Total	2063	$8,836,507	-0.5%	-3.7%	8.4%

Source: CapitalIQ

Short Selling in Biotech

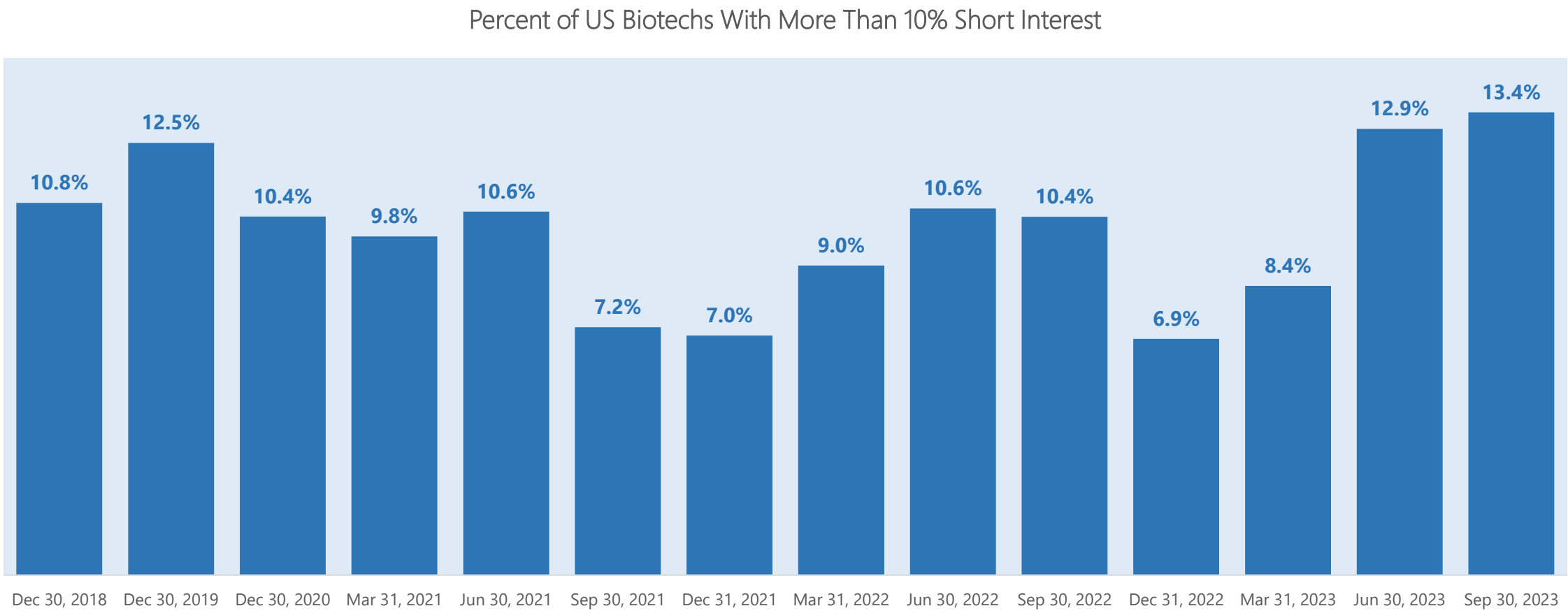
U.S. Biotech Short Interest at a High Point



Source: CapitalIQ and Stifel analysis. No lower market cap cutoff used for this analysis.

Over 13% of US Biotechs Have 10% or More Short Interest

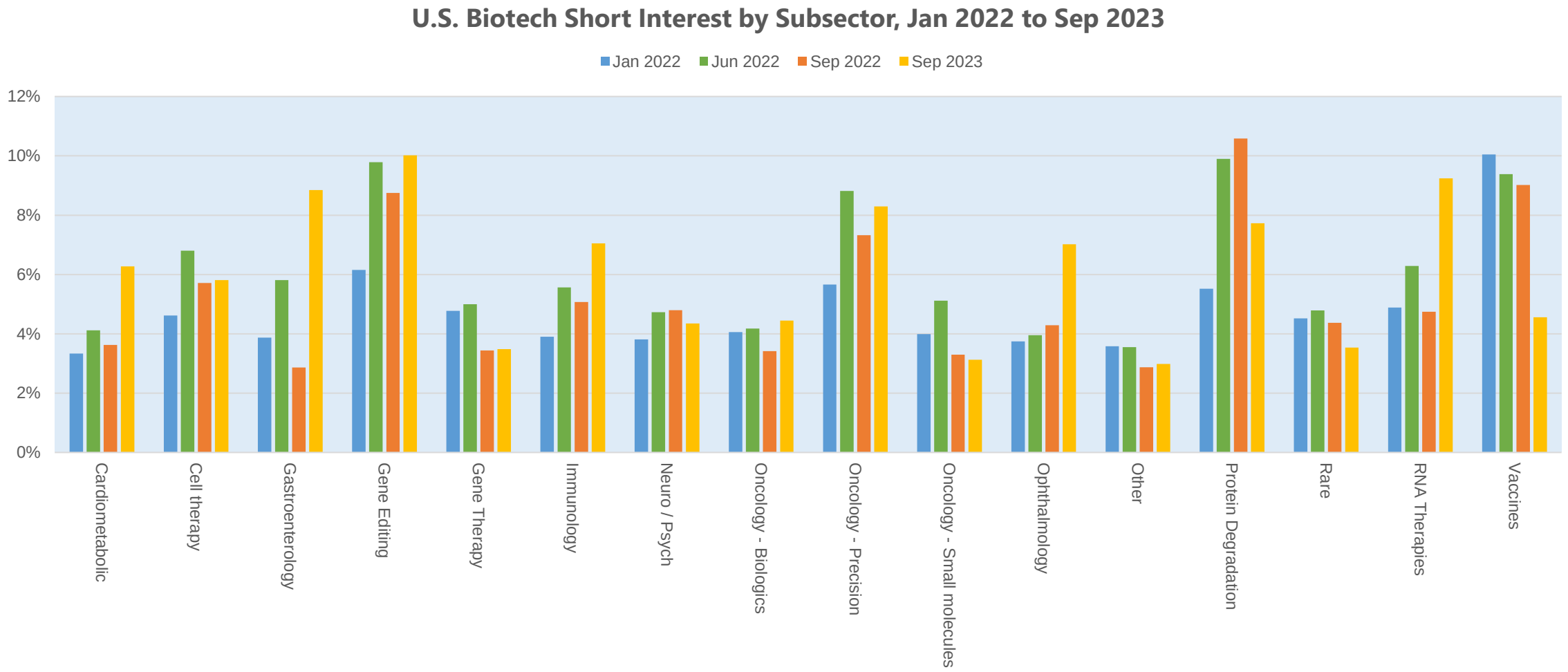
Today's biotech investor population includes quite a few skeptics. The number of biotechs with 10% or more short interest is at a high point.



Source: CapitalIQ and Stifel analysis. No lower market cap cutoff used for this analysis.

Short Interest by Subfield of Biotech, Jan 2022 to Present

Short interest has been dialed back in protein degraders, gastroenterology and vaccines. In contrast, shorting is up in cardio, immunology, ophthalmology and RNA therapeutics.



Source: CapitalIQ and Stifel Analysis.

Do Short Sellers Have a Clue?

There is a significant academic literature that says "yes". Short selling precedes negative returns. Portfolios of heavily shorted stocks underperform portfolios of less shorted stocks.

Boehmer, Ekkehart, Charles M. Jones, and Xiaoyan Zhang, 2008, Which shorts are informed? *Journal of Finance* 63, 491–527.

We construct a long daily panel of short sales using proprietary NYSE order data. From 2000 to 2004, shorting accounts for more than 12.9% of NYSE volume, suggesting that shorting constraints are not widespread. As a group, these short sellers are well informed. Heavily shorted stocks underperform lightly shorted stocks by a risk-adjusted average of 1.16% over the following 20 trading days (15.6% annualized). Institutional nonprogram short sales are the most informative; stocks heavily shorted by institutions underperform by 1.43% the next month (19.6% annualized). The results indicate that, on average, short sellers are important contributors to efficient stock prices.

Source: https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1540-6261.2008.01324.x

Jesse Blocher, 2020, Short Trading and Short Investing, *Journal of Empirical Finance.*

There is also a literature showing that short selling activity, defined as trades or trading volume labeled as short sales, predicts negative returns (e.g., Diether, Lee, and Werner (2009), Boehmer, Jones, and Zhang (2008)). Christophe, Ferri, and Angel (2004) identified short selling activity prior to earnings announcements is closely linked to post-announcement returns. Christophe, Ferri, and Hsieh (2010) find increased abnormal short activity prior to analyst downgrades and that this activity is related to post-downgrade returns. Engelberg, Reed, and Ringgenberg (2012) investigate short trade volume around news events.

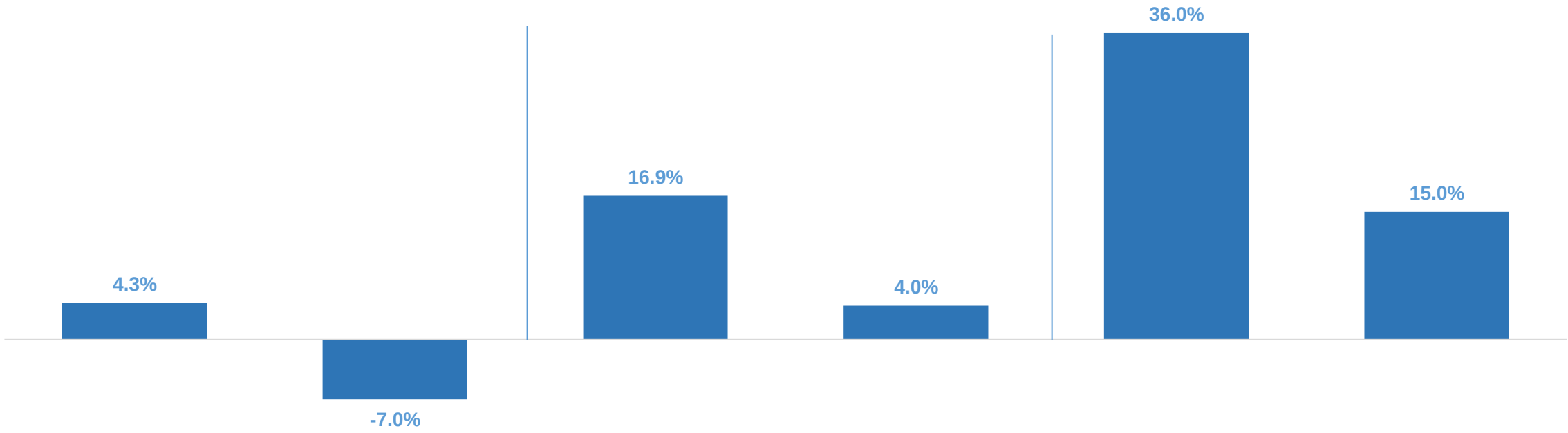
Source: https://www.sciencedirect.com/science/article/abs/pii/S092753982030061X

How About in Biotech? Is Short Selling Informative?

The answer in biotech is also yes. The share performance of biotech companies with 20% or higher short interest at the start of a year, on average, is significantly worse than that of biotech companies with 5% or less short interest at the start of the year. The average performance differences in 2022 and 2023 have been startlingly large. The chart below shows what you make if you shorted the most heavily shorted stocks each year and went long the least shorted stock.

Returns of a Equal-Weighted Portfolio that Shorts the Most Heavily Shorted U.S. Biotech Stocks in Next 12 Months While Going Long Stocks with Low Short Interest

(Heavily shorted stocks are those with 20% or more short interest at year start while low shor

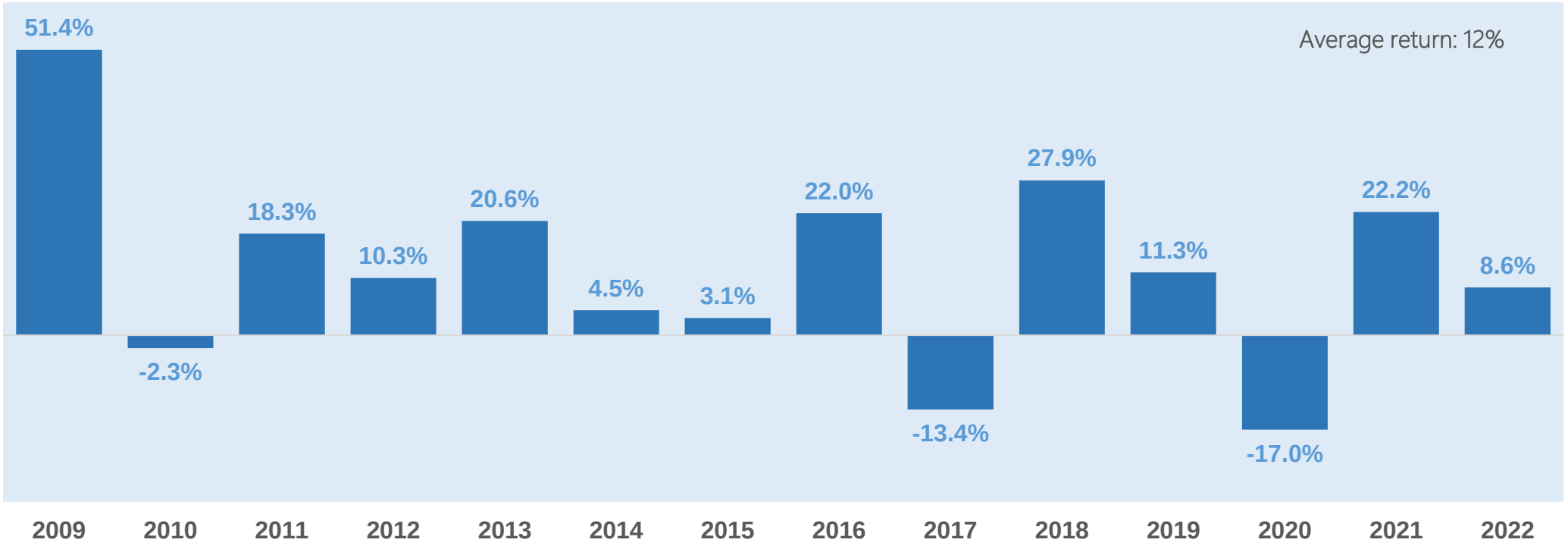


Source: CapitalIQ and Stifel analysis.

How About Short Newsletters?

The biotech short newsletter from Favus Institutional Research has shared its track record from recent years. The unaudited returns from following the recommendations have been positive. On average, an investor would have made 12% in aggregate from an equal weighted portfolio of Favus sell recommendations.

Average Return from Favus Institutional Research Biopharma Sell Recommendations
2009 to 2023 (from position open to position close)



Source: Favus Institutional Research (link: http://favusllc.com/)

Unaudited Returns from Scorpion Capital

Performance of every short we've published on from last close prior to publication through 3/27/23:

- 11/22 Twist Bioscience (NASDAQ: TWST) -57% vs. S&P +1%
- 5/22 IonQ (NYSE: IONQ) -35% vs. S&P -4%
- 10/21 Ginkgo Bioworks (NYSE: DNA) -90% vs. S&P -8%
- 9/21 Berkeley Lights (NASDAQ: BLI) -97% vs. S&P -10%
- 4/21 Quantumscape (NYSE: QS) -82% vs. S&P -3%
- 1/21 Nevro (NYSE: NVRO) -80% vs. S&P +6%

No longer updated, data as of 11/14/22 refresh:

- 12/19 Allakos (NASDAQ: ALLK) -94% vs. S&P +24%
- 12/18 Axogen (NASDAQ: AXGN) -56% vs. S&P +56%
- 8/18 Fanhua (NASDAQ: FANH) -81% vs. S&P +38%

Scorpion Capital specializes in investigative research on companies that they claim may be misrepresenting key factors to investors.

The company publicizes its findings to investors.

A recent article in the *California Management Review* termed Scorpion Capital an activist short seller.

The returns shown on the company's website would suggest that, on average, their short recommendations are associated with outsized performance.

Source: https://scorpioncapital.com/track-record

Do Short Sellers Benefit from Spreading False Rumors?

Engelberg et.al., "How are shorts informed?: Short sellers, news, and information processing," *Journal of Financial Economics*, Aug 2012, pp. 260-278.

There is now overwhelming evidence that short sellers are informed traders. When short interest or short volume are high, future returns are predictably low (see, e.g., Senchack and Starks, 1993, Asquith et al., 2005, Boehmer et al., 2008). Return predictability, however, suggests only that short sellers have an information advantage over other traders. In this paper, we ask *how* short sellers obtain that advantage.

To address this question, we combine a large archive of all corporate news events with a large panel of daily short selling. This unique combination allows us to comprehensively examine the relation between short selling and news events. We find that a substantial portion of short sellers' trading advantage comes from their ability to analyze publicly available information. In fact, while news events occur on only 22% of the days in our sample, these trading days account for over 45% of the total profitability from short selling.

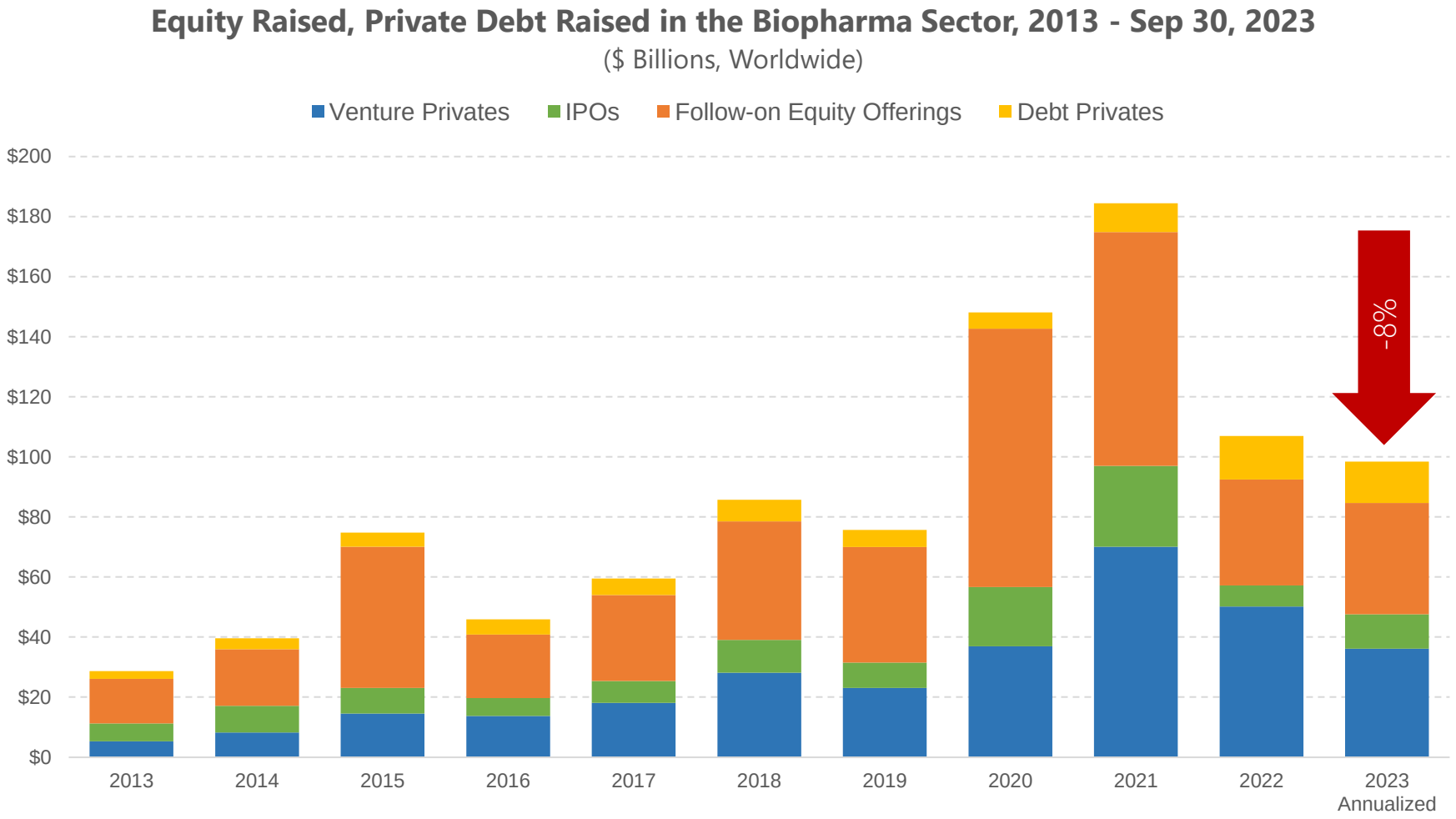
Although our evidence suggests that short sellers obtain an information advantage via superior information processing, some commentators have suggested other ways that short sellers achieve an advantage. The Securities and Exchange Commission (SEC) suggested that short sellers spread "false rumors" in an effort to manipulate firms "uniquely vulnerable to panic." If this type of manipulation were taking place, then it suggests that short sellers might initiate a trade and then spread rumors (see, e.g., van Bommel, 2003). In other words, we might expect to see short sellers trade before news events, even though the news events could turn out to contain false information.

We find little evidence to support the claim that short sellers' advantage comes from trading before information is released, even though short sellers have been shown to trade before the release of certain types of public information. For example, Karpoff and Lou (2010) show that short selling increases before the initial public revelation of firms' financial misrepresentation. Similarly, Christophe, Ferri, and Angel (2004) find evidence of informed short selling in the 5 days before earnings announcements.

Source: https://www.sciencedirect.com/science/article/abs/pii/S0304405X12000384

Capital Markets and Deals Environment

Overall Biopharma Capital Raised To Date In 2023 Is Down 8% Versus 2022 (On an Annualized Basis)



Venture private volumes and follow-on equity volumes this year have been down modestly compared to 2022.

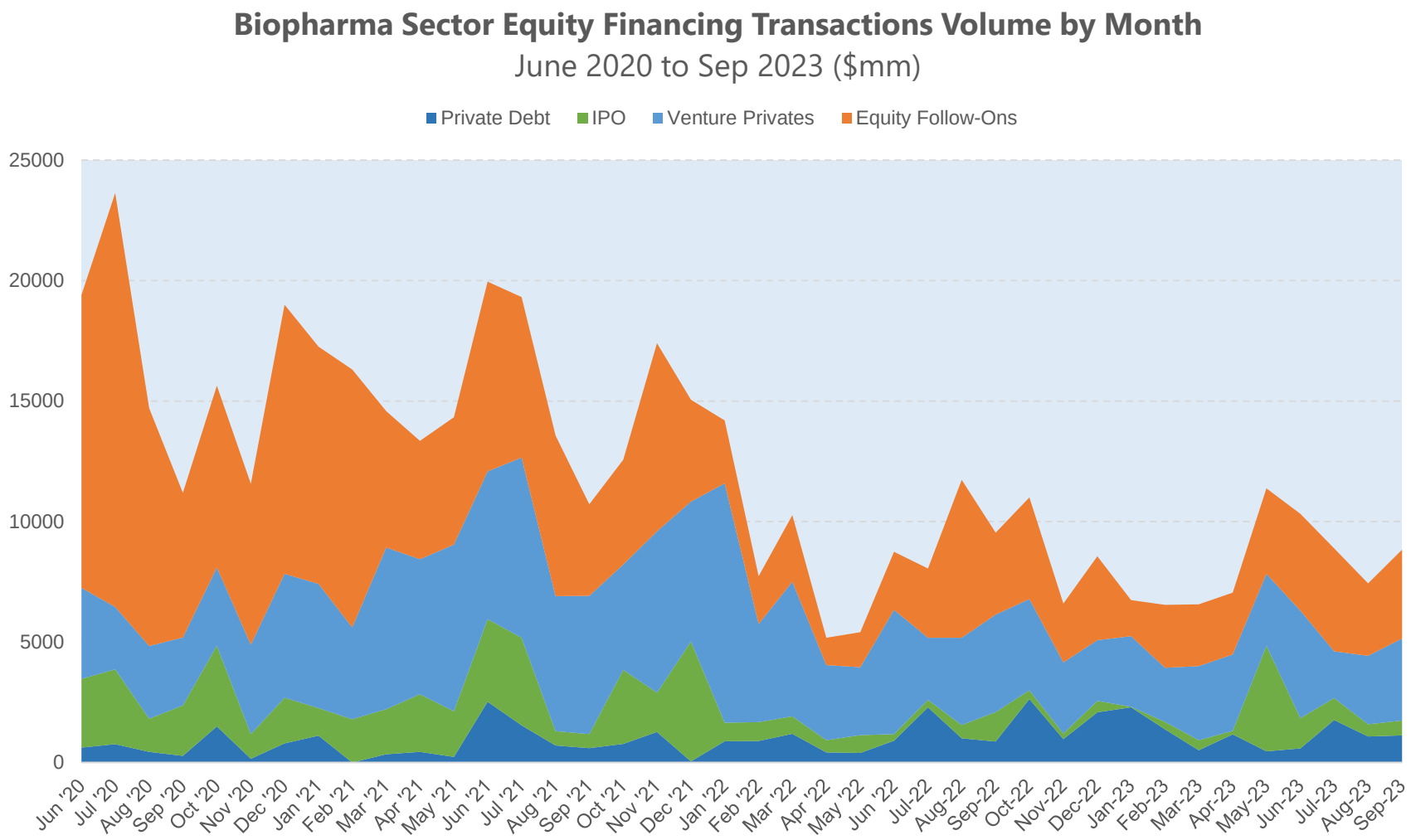
The markets have been materially weaker in 2023 than in 2021 and 2022.

The pace of capital raising in 2023 exceeds that of all years prior to 2020.

We have returned to a Pre-Pandemic type fundraising environment.

Source: CapitalIQ and Stifel research

Monthly Biopharma Market Capital Raise Data Shows Pick Up in Activity Starting in May 2023



While volumes are down somewhat in 2023 versus 2022 it is apparent in this chart that the capital market picked up in April 2023 and has stayed at a heightened issuance level since then.

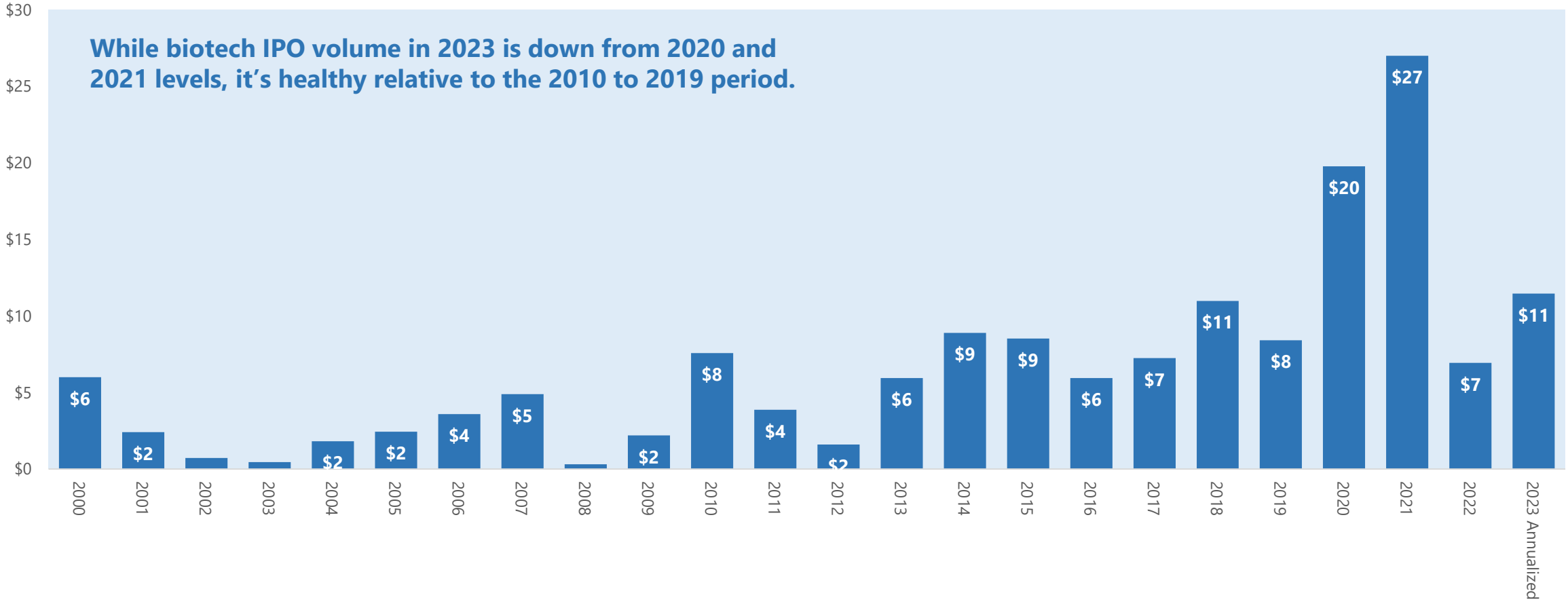
Nonetheless, current issuance volumes remain well down from levels seen during the Pandemic.

Source: CapitalIQ and Stifel research

Annualized 2023 Global Biotech IPO Volume Up 65% From 2022 and Down 58% Versus 2021

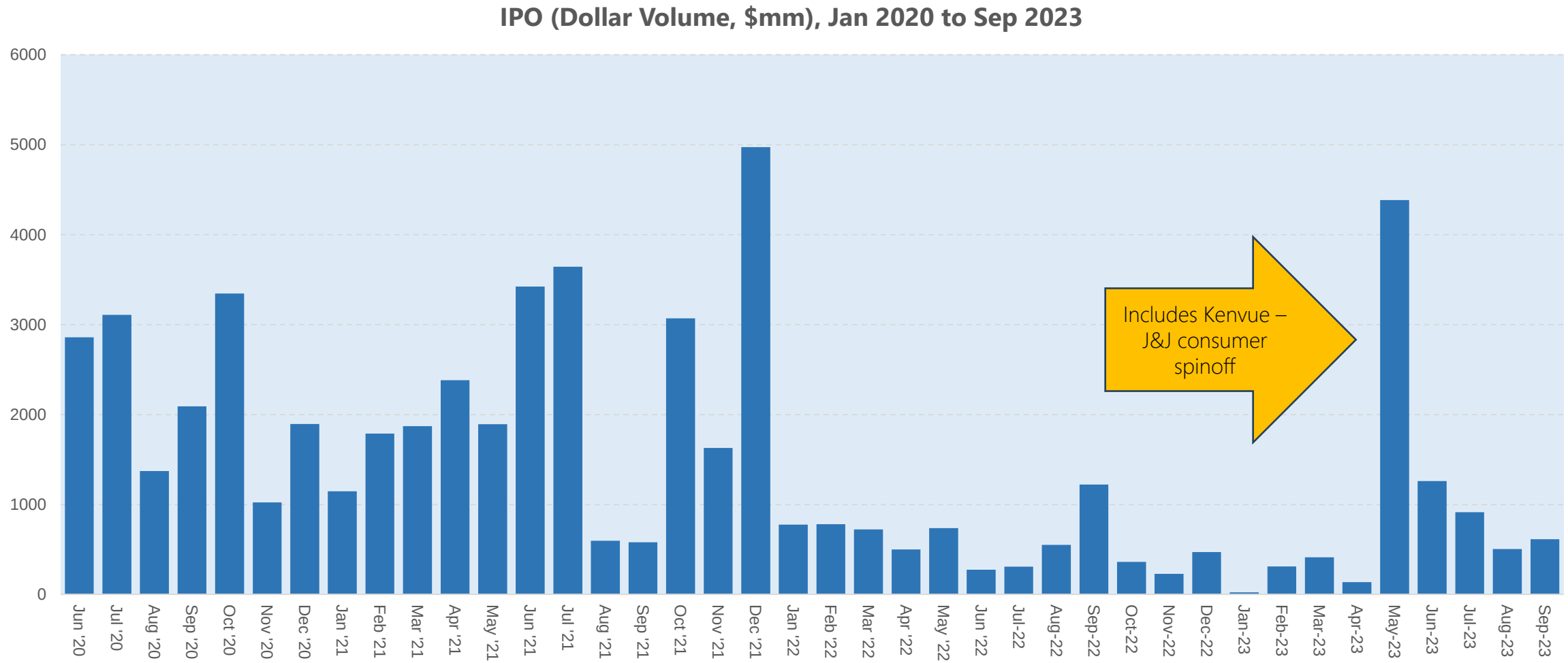
Global IPO Volume in the Biopharma Sector, 2000 - Sep 30, 2023

($ Billions, Worldwide)



Source: CapitalIQ.

Monthly Global Biopharma IPO Volume Soft Versus May to July Period



Source: CapitalIQ.

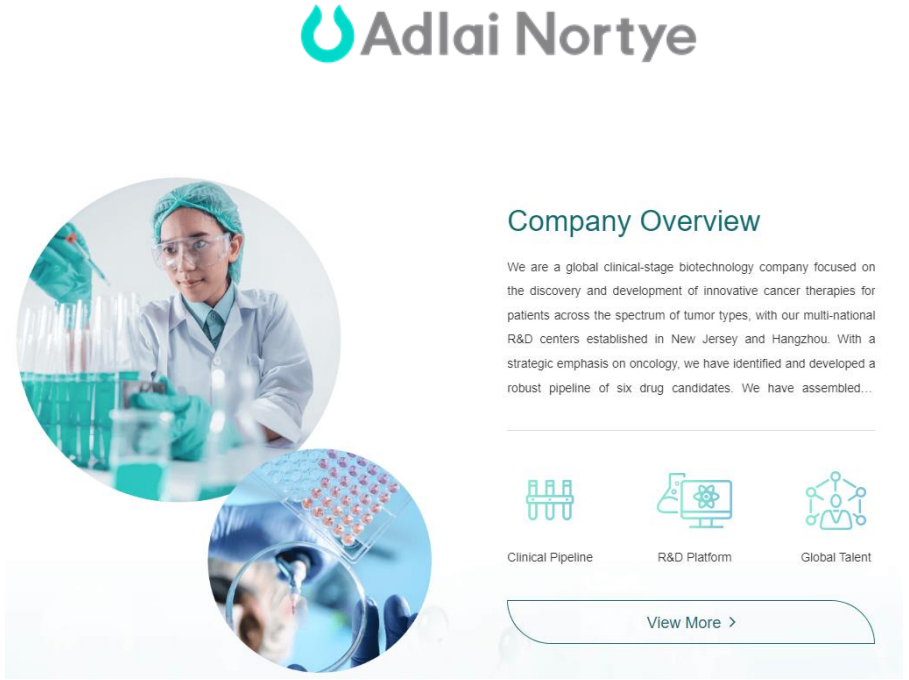
Adlai Nortye IPO Gives Old Novartis Cancer Drug New Life

Ben Fidler, *Biopharma Dive*, Sep 29, 2023 (excerpt)

Cancer drug developer Adlai Nortye on Thursday raised $57.5 million in an initial public offering, becoming the 16th biotechnology company to debut on a U.S. stock exchange this year, according to BioPharma Dive data.

The company sold 2.5 million shares at $23 apiece — a smaller offering than it had pitched in early August. Nippon Kayaku, a licensing partner and Japan-based pharmaceutical manufacturer, also agreed to acquire $40 million in additional shares in a concurrent private financing deal, according to a regulatory filing.

The offering will fund the development of a targeted cancer drug once owned by Novartis. That medicine, formerly known as buparlisib and now AN2025, is in late-stage trials for a form of head and neck cancer and in earlier testing against other solid tumors.



Source: https://www.reuters.com/markets/deals/schott-pharma-debuts-frankfurt-stock-exchange-2023-09-28/

Schott Pharma Shares Jump 16% in Frankfurt Trading Debut

Reuters, Sep 28, 2023 (excerpt)

FRANKFURT/LONDON, Sept 28 - Shares in medical vials manufacturer Schott Pharma rose 16% in their trading debut on Thursday in Germany's largest initial public offering (IPO) so far this year.

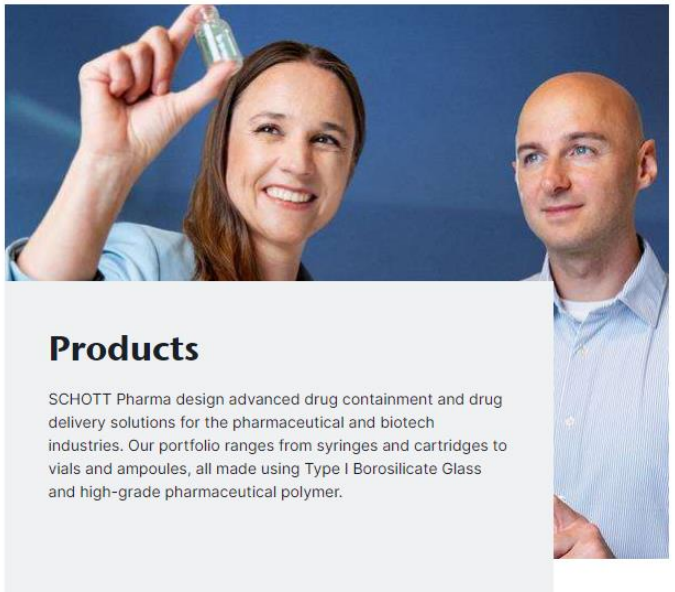
Shares in the company closed at 31.30 euros ($33.08) in Frankfurt, up from the 27 euros paid by investors in the IPO, adding to signs that Europe's IPO market is picking up.

Schott Pharma, a unit of Schott AG, has said the IPO, which counts Qatar Investment Authority (QIA) as a cornerstone investor, could raise up to 935 million euros ($982.50 million).

"It is a super start in the reopening of the IPO market after the summer," said Christoph Heuer, co-head of equity capital markets (ECM) for Northern Europe at BNP Paribas, one of the banks leading the deal.

"The market has been challenging to navigate in the last two weeks, but investors were convinced of the equity story."

SCHOTT



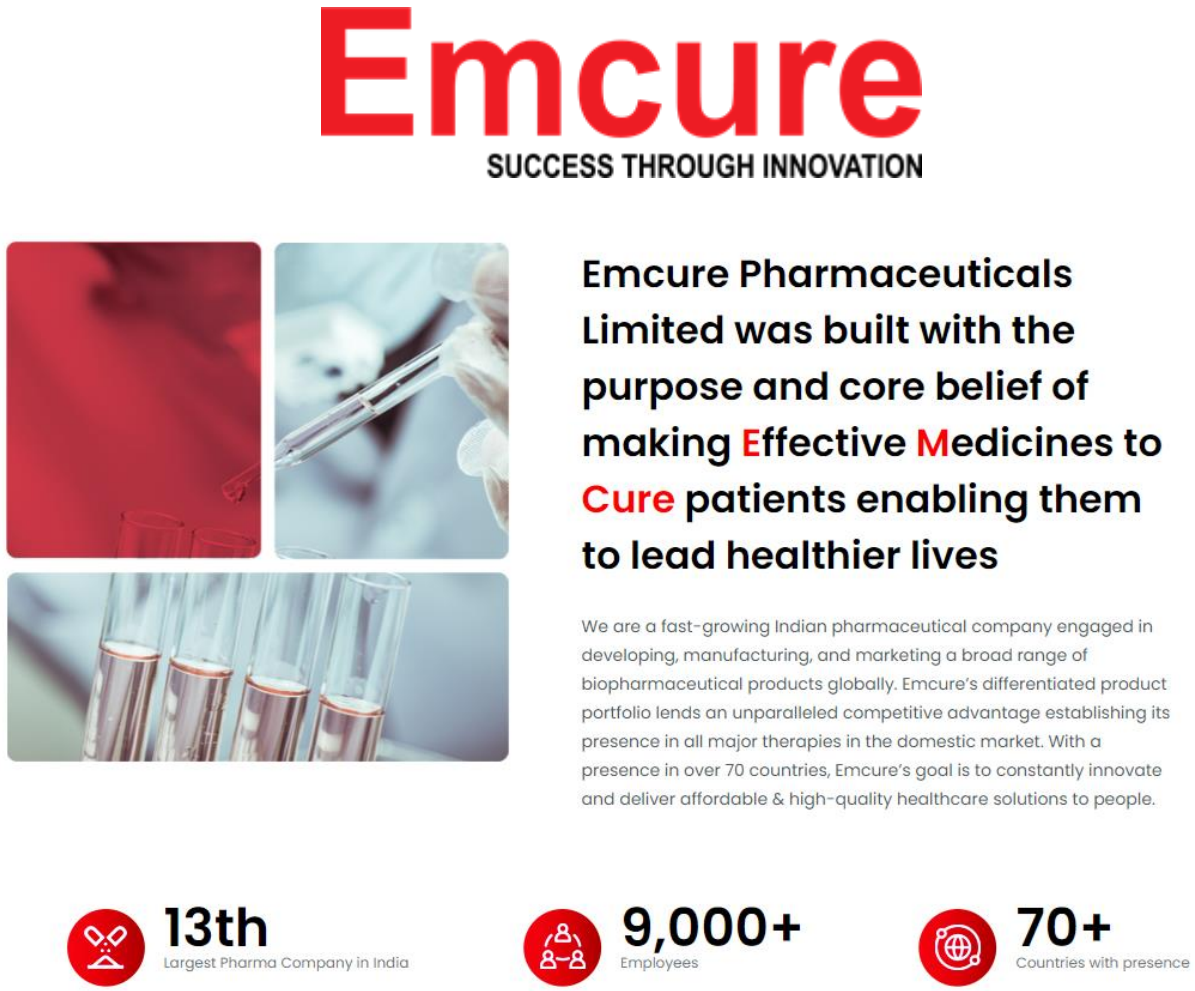
Source: https://www.reuters.com/markets/deals/schott-pharma-debuts-frankfurt-stock-exchange-2023-09-28/

India's Emcure Pharma plans 2024 IPO

Reuters, Sep 25, 2023 (excerpt)

Mumbai, Sept 25 - India's Emcure Pharmaceuticals aims to raise $400-$500 million from an initial public offering planned for next year, two sources said, reviving listing plans the drugmaker shelved in early 2022 as the Ukraine war roiled global markets.

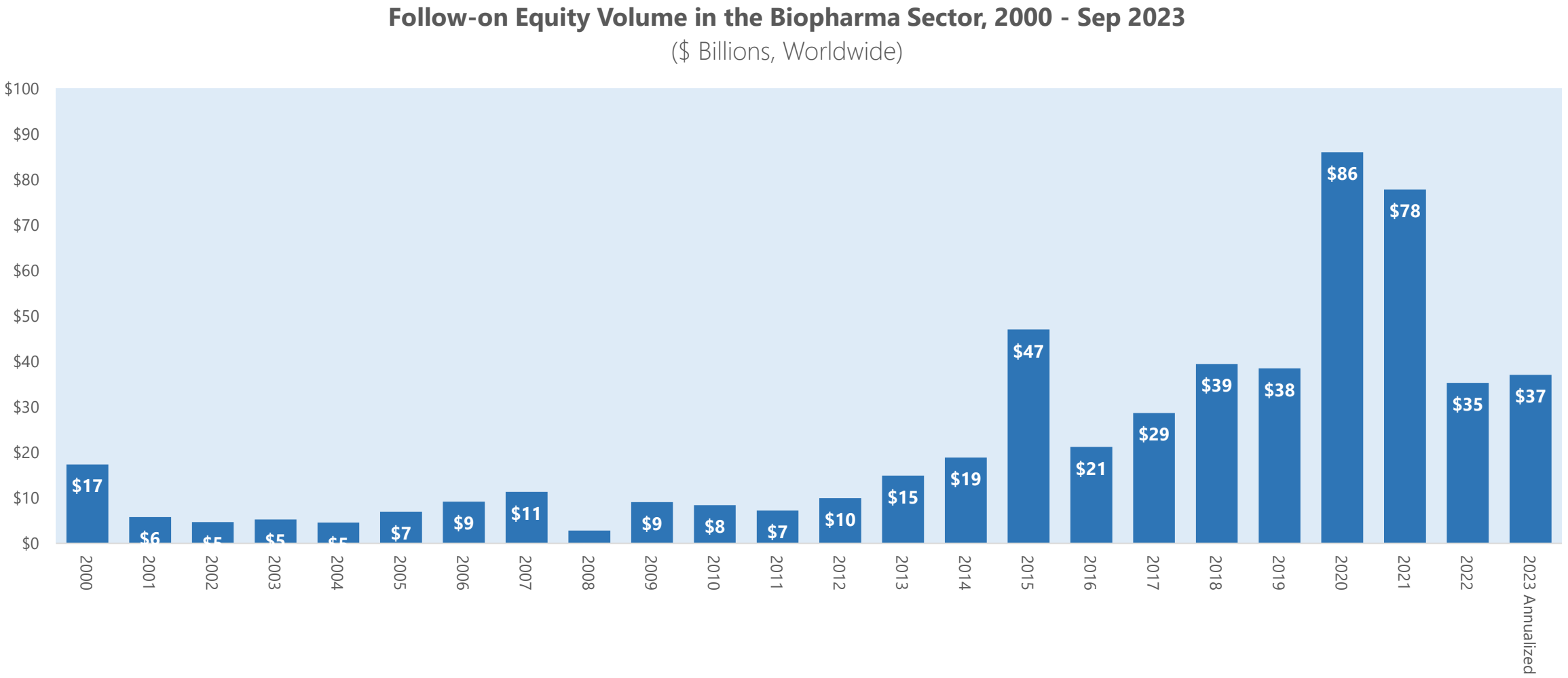
Emcure, backed by private equity firm Bain Capital is targeting a valuation of about $3 billion, both sources with direct knowledge of the matter said.



Source: https://www.reuters.com/markets/deals/indias-emcure-pharma-plans-2024-ipo-hires-jp-morgan-jefferies-sources-2023-09-25/

Annualized 2023 Global Follow-On Equity Volume Up 5% From 2022 and Down 52% Versus 2021

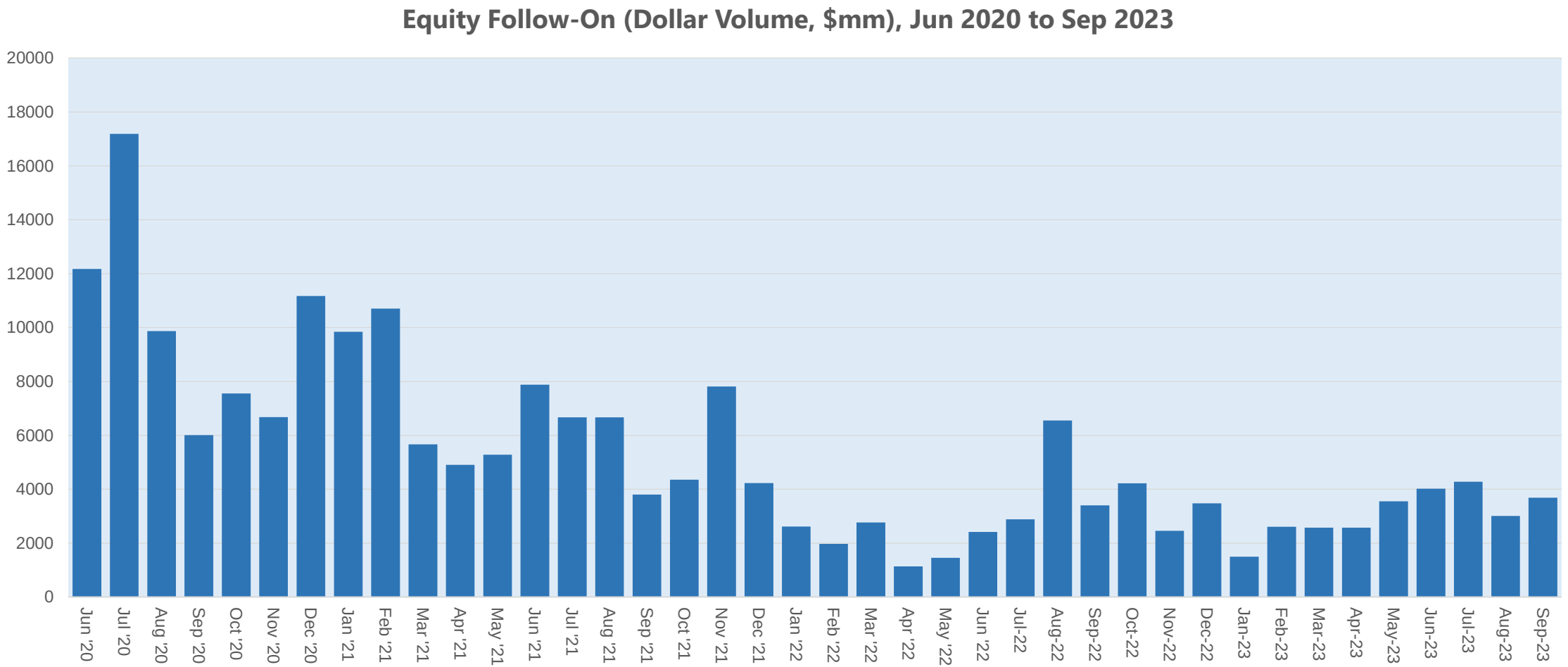
Looking back, the 2022 to 2023 follow-on equity market looks very similar volume-wise to the markets of 2018 and 2019.



Source: CapitalIQ and Stifel research

Monthly Global Biopharma Follow-On Volume Steady in Recent Months

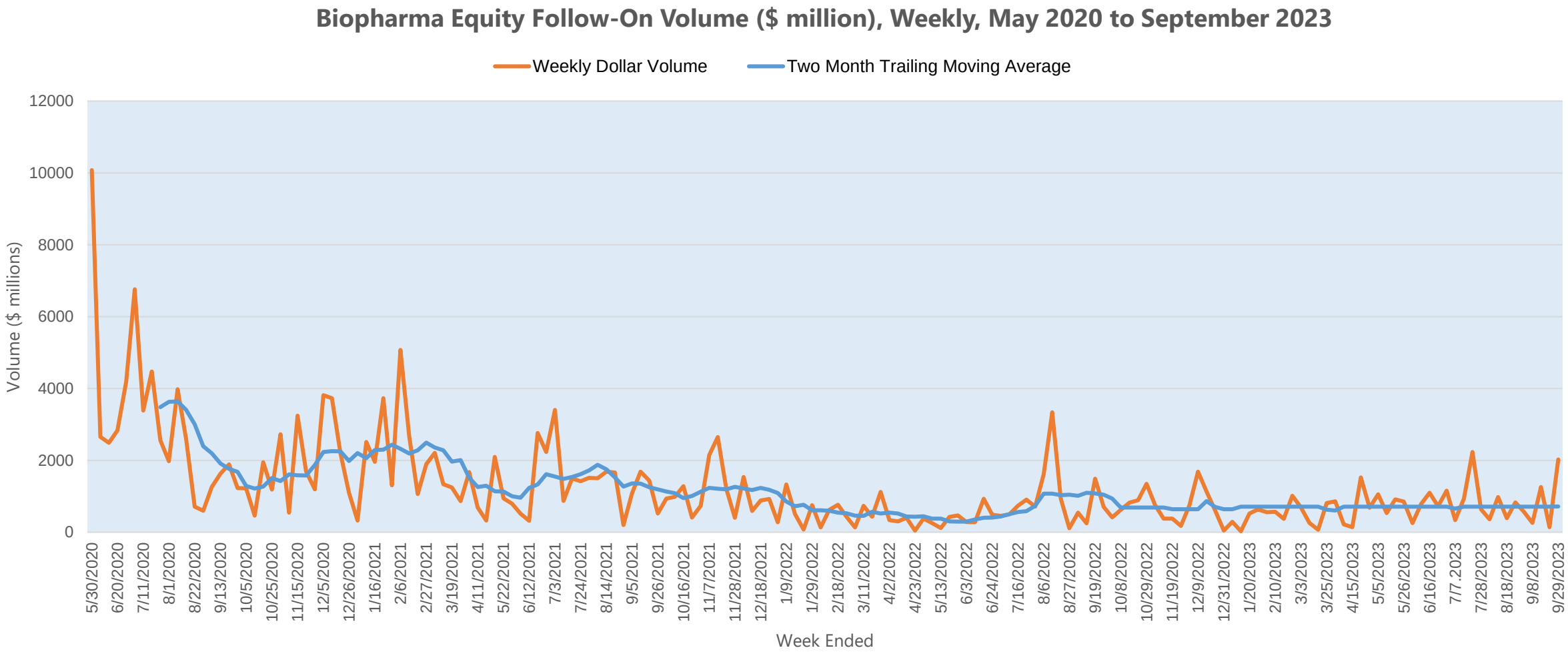
The follow-on market has been steady in the last eight months. September was not an exception.



Source: CapitalIQ.

Last Week Was Strong for Follow-On Offerings

Last week saw $2 billion in follow-on volume. This was the second strongest week of the year.



Source: Data from CapitalIQ and Stifel research.

Madrigal Pharmaceuticals Announces Pricing of $500 Million Public Offering

CONSHOHOCKEN, Pa., Sept. 28, 2023 (GLOBE NEWSWIRE) - Madrigal Pharmaceuticals, Inc. (Nasdaq: MDGL), a clinical-stage biopharmaceutical company pursuing novel therapeutics for nonalcoholic steatohepatitis (NASH), today announced the pricing of its underwritten public offering of 1,248,098 shares of its common stock at a public offering price of $151.69 per share, and, to certain investors, pre-funded warrants to purchase 2,048,098 shares of common stock at a price of $151.6899 per pre-funded warrant, which represents the per share public offering price for the common stock less the $0.0001 per share exercise price for each such pre-funded warrant. The gross proceeds to Madrigal from the offering, before deducting the underwriting discounts and commissions and other estimated offering expenses, are expected to be approximately $500 million. Madrigal has granted the underwriters of the offering a 30-day option to purchase up to an additional 494,429 shares of common stock from the company at the public offering price, less underwriting discounts and commissions.

Madrigal intends to use the net proceeds from this offering for its clinical and commercial activities in preparation for a potential launch of resmetirom in the U.S. and for general corporate purposes, including, without limitation, research and development expenditures, clinical trial expenditures, manufacture and supply of drug substance and drug products, potential acquisitions or licensing of new technologies, capital expenditures and working capital.

Source: https://ir.madrigalpharma.com/news-releases/news-release-details/madrigal-pharmaceuticals-announces-pricing-500-million-public

Structure Raises $300M as Oral GLP-1 Drug's Data Keep Up With Pfizer, Eli Lilly

Preliminary weight loss and safety data for Structure Therapeutics' drug candidate suggest it's competitive with other oral GLP-1 targeting contenders from big pharma companies. The data are from a small study and a short time frame, but Structure was able to leverage the encouraging preliminary results into a private placement of securities.

By FRANK VINLUAN

Post a comment / Sep 29, 2023 at 3:03 PM

Structure Therapeutics' lead drug candidate is chasing big pharmaceutical rivals in the race for new oral weight-loss medications, and the company had been telling investors to expect data late this year from an early-stage study and a mid-stage clinical trial. A snafu is delaying the mid-stage study, but the early-stage trial has preliminary data suggesting Structure's molecule could be competitive with others, results enabling the company to raise $300 million in new capital.

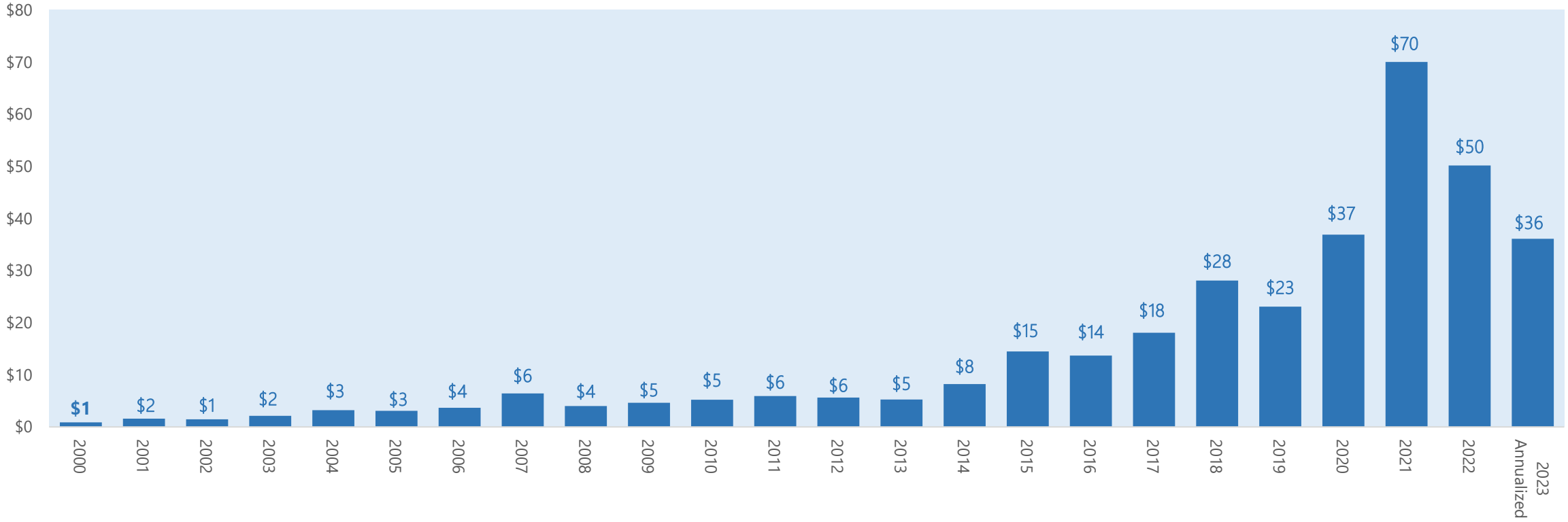
The Structure drug, GSBR-1290, binds to GLP-1, the same receptor targeted by Novo Nordisk products Ozempic and Wegovy as well as Mounjaro from Eli Lilly. Those large molecule biologics are administered as injections. Structure's small molecule drug could offer patients the convenience of a once-daily pill.

Source: https://medcitynews.com/2023/09/oral-glp1-drug-obesity-weight-loss-structure-therapeutics-pfizer-eli-lilly/

Annualized 2023 Global Venture Equity Volume Down 28% From 2022 and Down 58% Versus 2021

Volume in the privates market is down 48% from 2021 and 28% from 2022. Venture investors are stretching out their dollars in light of the weaker investment environment. Volume in 2023 is on par with what was seen in 2020 and is ahead of all prior years.

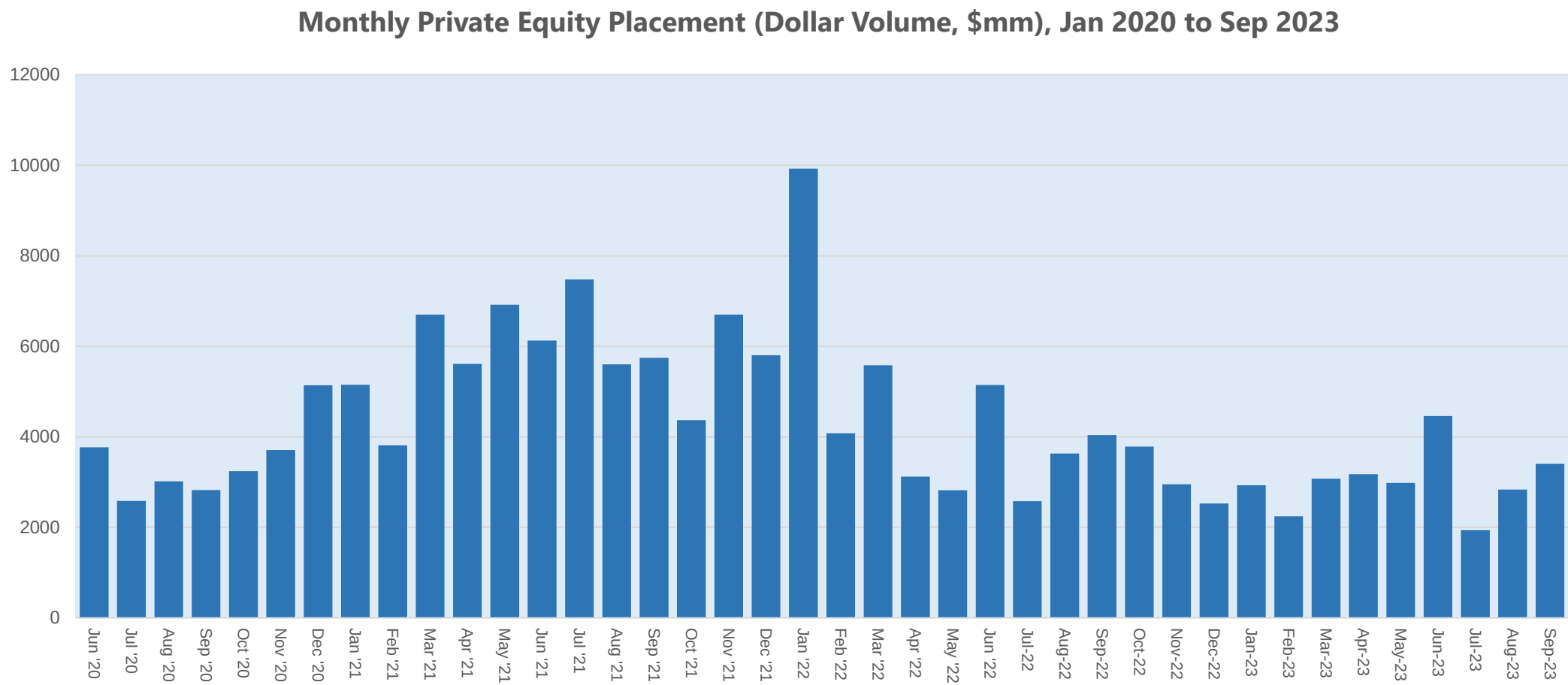
Venture Privates in the Biopharma Sector, 2000 – September 2023
(Dollar Volume, $Billions, Worldwide)



Source: CapitalIQ.

Monthly Global Biopharma Venture Equity Volume Steady in Recent Months

September saw a reversal in the recent downtrend in the venture equity biopharma market. Dollar volume of privates in September was the second strongest in twelve months.



Source: CapitalIQ and Crunchbase.

Despite a Summer of Blockbuster Rounds, Biotech Funding is on Track to Level Off at Pre-pandemic Norms

Max Gelman, *Endpoints News*, Sep 28, 2023 (excerpt)

"It might appear as though the private biotech sector is approaching a thaw. In recent weeks, a Flagship startup raised $273 million, an RNA company put together $200 million, and even a preclinical radiopharmaceutical biotech secured $175 million.

But under the microscope, the reality is much more complicated.

Private biotech financing has remained largely flat for much of the year, according to PitchBook data as of Monday. The sector pulled in roughly $5 billion each quarter in 2023. That's high compared to historical levels, Atlas Venture partner Bruce Booth tells *Endpoints News*, but well below the Covid-19 pandemic boom years of 2020 and 2021.The third quarter is on track for 12 raises surpassing the $100 million mark, which is the same as in the first quarter and one fewer than in the second quarter. That said, nine of those raises came in the last six weeks.

The plateau counters the better-times-are-coming vibes that have circulated in recent weeks and point to a world in which investors appear to be much more disciplined than they were roughly two years ago."

Source: https://endpts.com/despite-a-summer-of-blockbuster-rounds-biotech-funding-is-on-track-to-level-off-at-pre-pandemic-norms/

Largest Biotech Venture Rounds, 2023 Year-to-Date

Announced	Company	Amount ($mm)	Round	Lead Investor	Stage at Funding	Primary TA	Primary Tech
5/16/2022	Kriya Therapeutics	$430	Series C	Patient Square Capital	02 Preclinical / IND	Endocrine / Metabolic	Gene Therapy
5/24/2023	ElevateBio LLC	$401	Series D	AyurMaya	01 Platform / Discovery	Cancer	Cell Therapy
5/23/2023	ReNAgade Therapeutics Inc.	$300	Series A	MPM Capital	01 Platform / Discovery	Unknown	RNA
9/14/2023	Generate Biomedicines	$273	Series C	Flagship	03 Phase I	Infectious	AI
4/26/2023	Orbital Therapeutics Inc.	$270	Series A	ARCH Venture Partners	01 Platform / Discovery	Autoimmune	RNA
9/19/2023	ReCode Therapeutics	$250	Series B	Pfizer Venture Investments	02 Preclinical / IND	Pulmonary	RNA
9/06/2023	Apollo Therapeutics LLP	$227	Series C	Patient Square Capital	03 Phase I	Inflammation	Immunotherapy
8/21/2023	Genesis Therapeutics Inc.	$224	Series B	Andreessen Horowitz (aka a16z)	01 Platform / Discovery	Not Applicable	AI
9/06/2023	Nimbus Therapeutics Inc.	$210	Unspecified	GV (Google Ventures, Alphabet)	04 Phase II	Endocrine / Metabolic	Small Molecule
3/01/2023	CARGO Therapeutics Inc.	$200	Series A	Third Rock Ventures LLC	03 Phase I	Cancer	Cell Therapy
8/09/2023	ADARx Pharmaceuticals Inc.	$200	Series C	Bain Capital Life Sciences	01 Platform / Discovery	Endocrine / Metabolic	RNA
8/21/2023	CapGenesis Therapeutics	$200	Series B	NA	04 Phase II	Other	Small Molecule
2/16/2023	Aera Therapeutics Inc.	$193	Series B	ARCH Venture Partners	01 Platform / Discovery	Unknown	Protein
9/07/2023	Mariana Oncology	$175	Series B	Deep Track Capital	01 Platform / Discovery	Cancer	Radiotherapy
9/27/2023	Avalyn Pharma Inc.	$175	Series C	Perceptive Xontogeny Venture Fund	06 Approved	Pulmonary	Small Molecule
4/13/2023	TORL BioTherapeutics LLC.	$158	Series B	Goldman Sachs Asset Management	03 Phase I	Cancer	Antibody
3/27/2023	ArriVent Biopharma Inc.	$155	Series B	Sofinnova Investments Inc.	03 Phase I	Cancer	Protein
8/17/2023	Abcuro Inc.	$155	Series B	Redmile Group	03 Phase I	Autoimmune	Immunotherapy
6/29/2023	Worg Pharmaceuticals	$152	Series C	NA	04 Phase II	Inflammation	Immunotherapy
1/18/2023	Pathalys Pharma Inc.	$150	Series A	Abingworth Management Ltd.	05 Phase III	Renal	Small Molecule
5/25/2023	Carmot Therapeutics Inc.	$150	Series E	Deep Track Capital	04 Phase II	Cancer	Small Molecule
6/05/2023	Alkeus Pharmaceuticals Inc.	$150	Series B	Bain Capital Life Sciences	04 Phase II	Ophthalmic	Small Molecule
7/11/2023	Septerna Inc.	$150	Series B	RA Capital Management LLC	01 Platform / Discovery	Neurologic	Small Molecule
8/23/2023	Rapport Therapeutics Inc.	$150	Series B	Cormorant Asset Management	03 Phase I	Neurologic	Protein

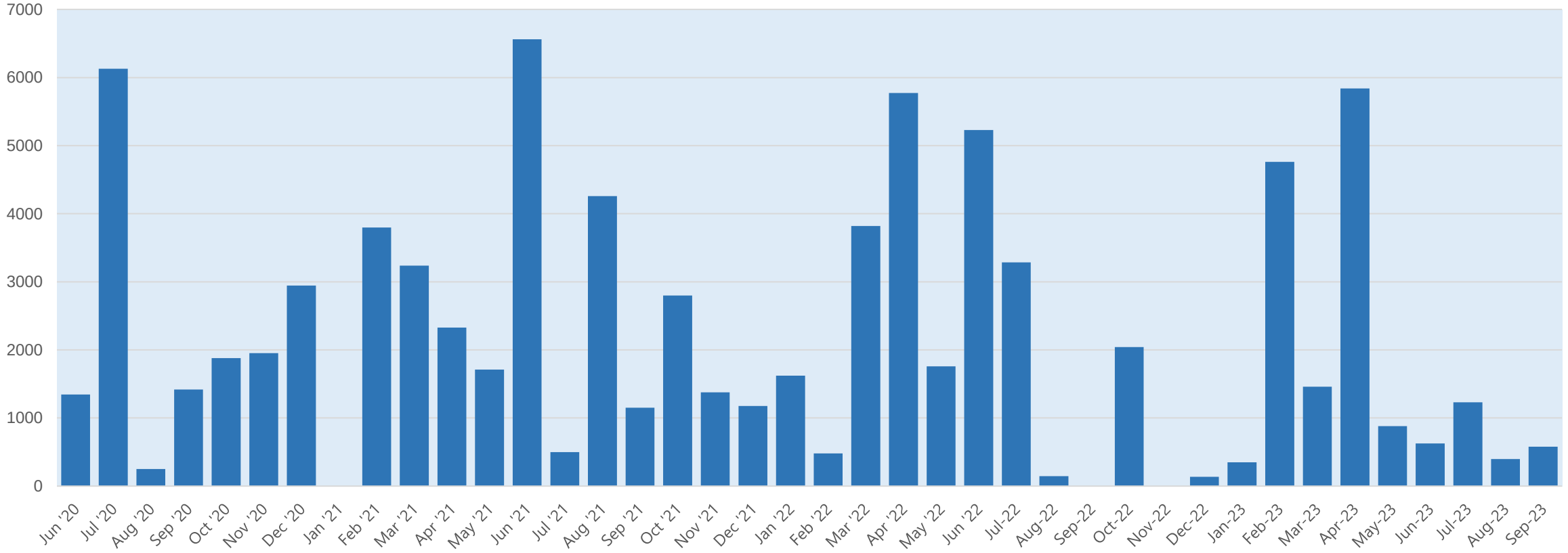
Source: DealForma, Jan 1, 2023 to Sep 30, 2023

Monthly Global Biopharma Venture Fund Raises

Venture funds raised $400mm in August and $570mm in September. The pace is well below what was seen in 2021 and 2022. The largest recent fund close was a $500mm raise by Sofinnova Investments filed in September with the SEC.

Capital Raised by Biopharma Focused Venture Funds

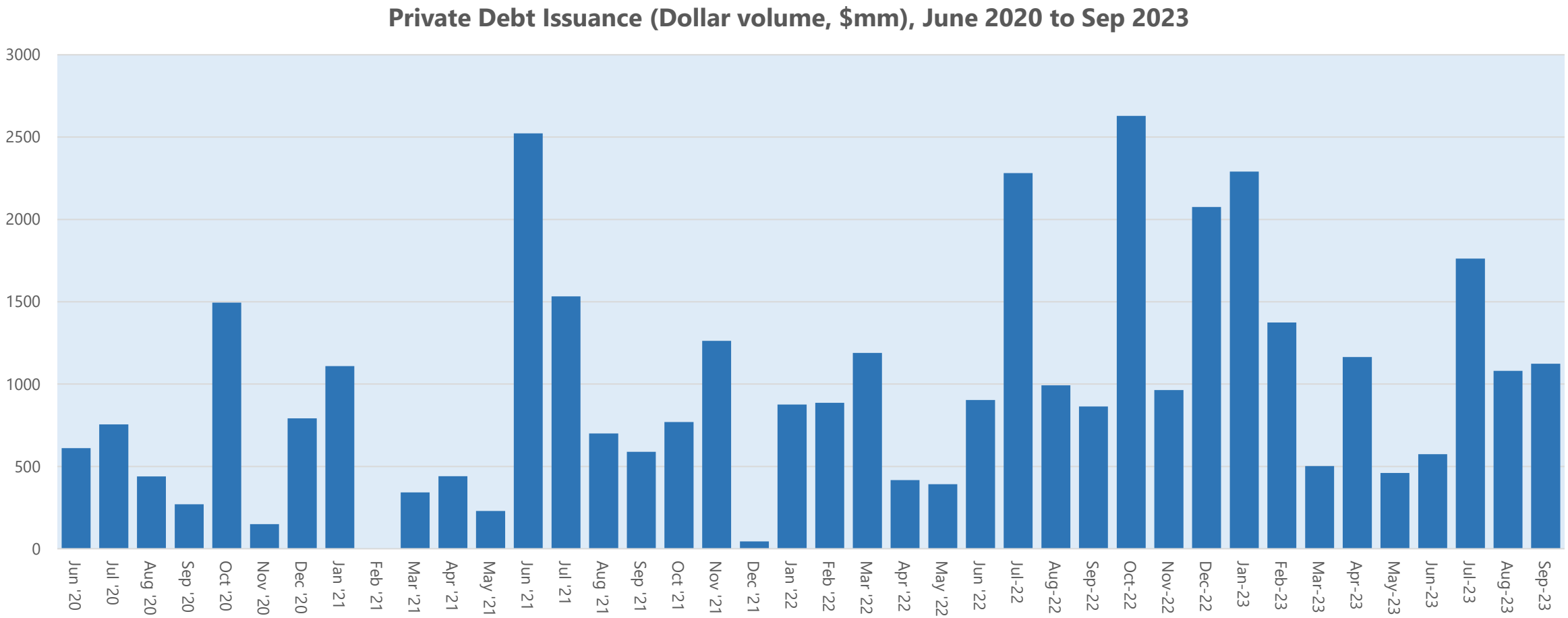
(Dollar Volume, $mm), Jan 2020 to Sep 2023



Source: Biospace and Stifel Research.

Monthly Global Biopharma Private Debt Volume Steady in Recent Months

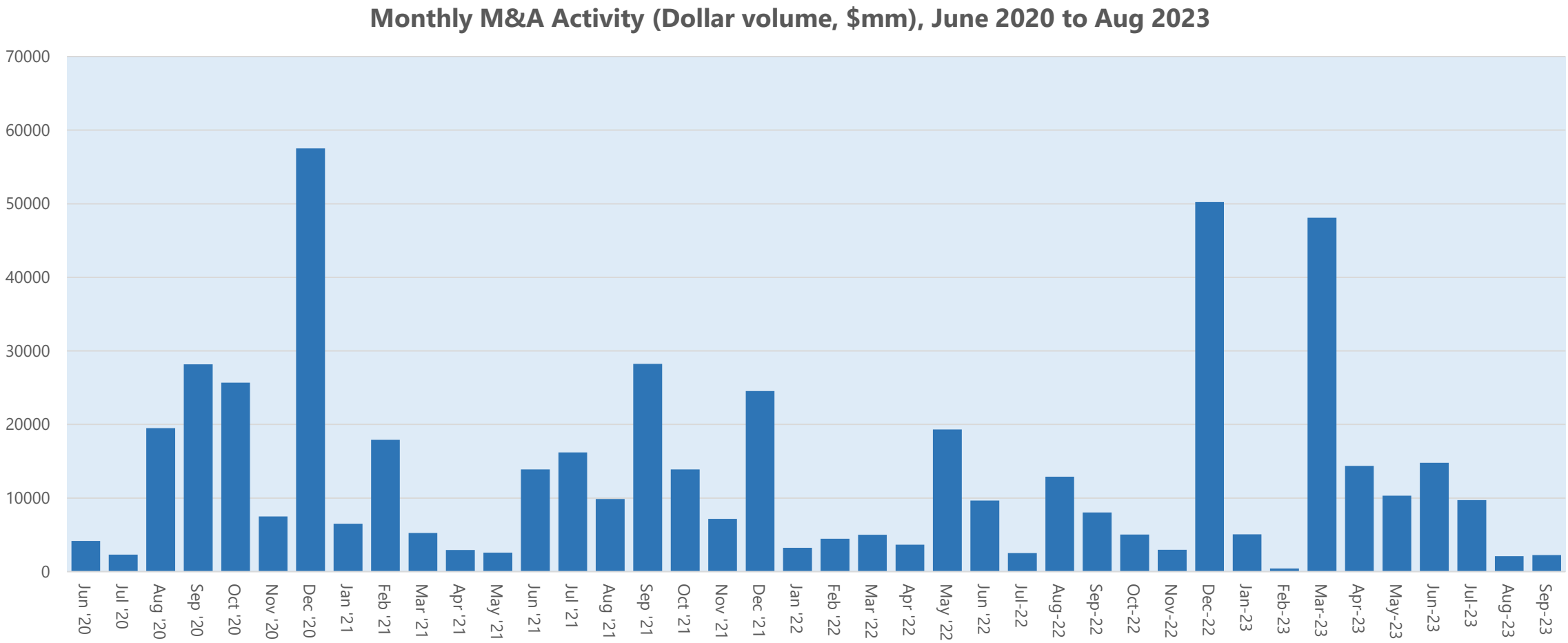
Private debt market has been strong in recent months despite high rates. September saw $1bn in volume.



Source: CapitalIQ.

Monthly M&A Volume Way Down Versus First Half of the Year

M&A volume has been exceptionally quiet in August and September. This is in sharp contrast to the March to July period.



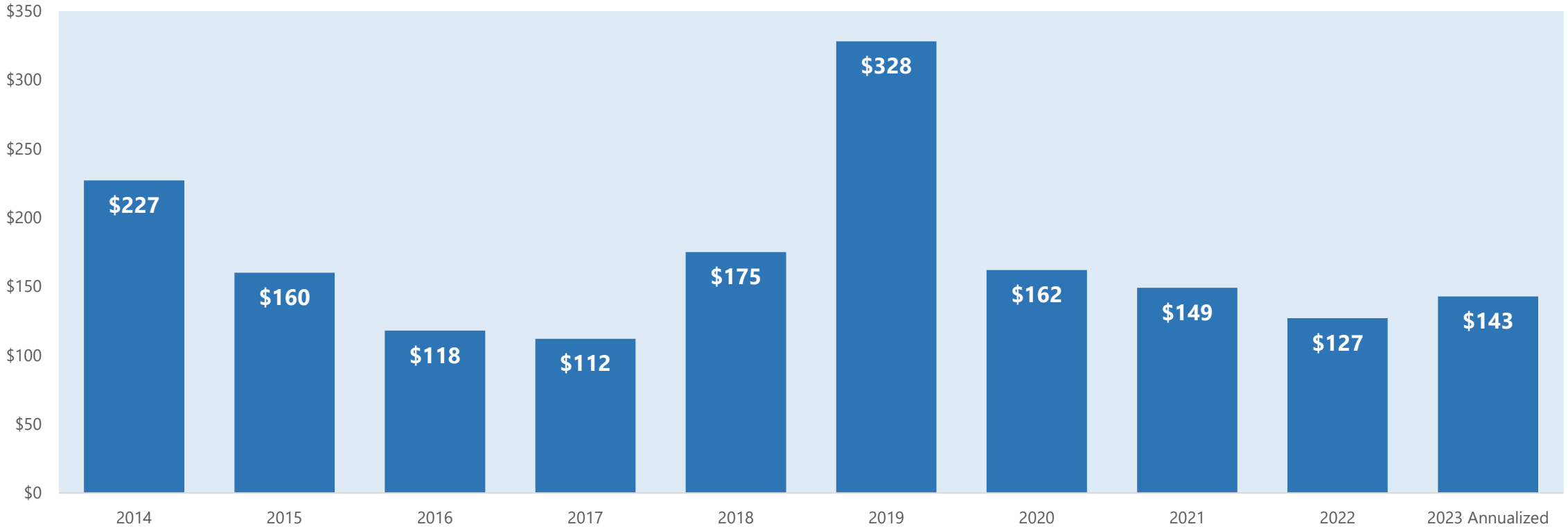
Source: CapitalIQ and DealForma.

Annualized 2023 M&A Volume Up 12% From 2022 and Down 4% Versus 2021

After the first half of the year, we were on track for 2023 to be the second busiest biopharma M&A year on record. That has all changed now. With very quiet volume in the last sixty days, we are looking at an annualized volume pace of $143 billion. While ahead of 2022, this would be considered a middling year for volume considering historical precedent.

M&A Volume in the Biopharma Sector, 2014 - Sep 30, 2023

($ Billions, Worldwide)



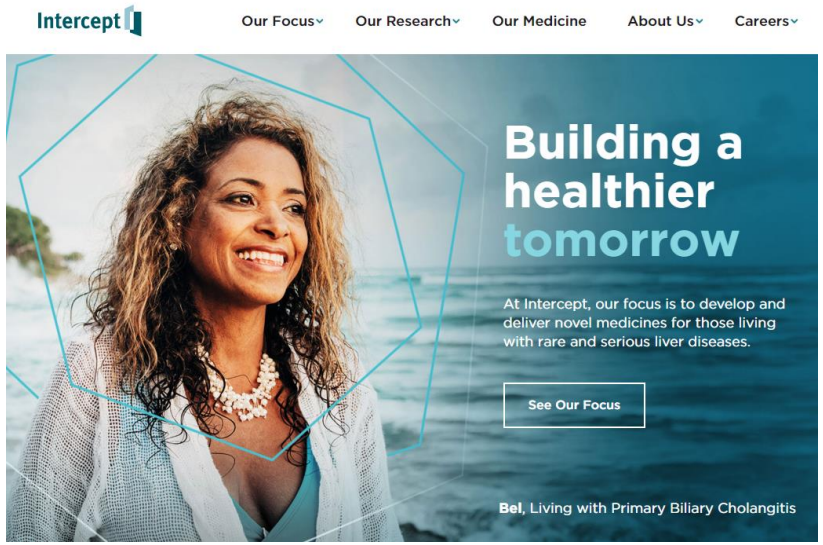
Source: CapitalIQ and DealForma.

Alfasigma to Acquire Intercept Pharma for $840mm Upfront

BOLOGNA, Italy and MORRISTOWN, N.J., Sept. 26, 2023 (GLOBE NEWSWIRE) -- Alfasigma S.p.A ("Alfasigma"), one of Italy's leading pharmaceutical companies, and Intercept Pharmaceuticals, Inc. (Nasdaq: ICPT, "Intercept"), a leading biopharmaceutical company in rare and serious liver diseases, today announced that they have entered into a definitive merger agreement under which Alfasigma has agreed to acquire Intercept for $19.00 per share in cash. The anticipated transaction will materially expand Alfasigma's gastrointestinal and hepatology portfolio and its presence in the U.S. market.

Intercept's lead medicine is Ocaliva® (obeticholic acid), a farnesoid X receptor agonist approved in the United States and several other jurisdictions for the treatment of primary biliary cholangitis ("PBC") in combination with ursodeoxycholic acid ("UDCA") in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA. Ocaliva® is the only approved second-line therapy for PBC and has experienced double-digit year-over-year growth supported by an experienced specialty sales force and strong prescriber base. Intercept also benefits from a broader clinical development pipeline anchored by a novel fixed-dose combination of obeticholic acid and bezafibrate in phase 2 trials for PBC.

Under the terms of the merger agreement, Alfasigma has agreed to commence a cash tender offer to acquire all issued and outstanding shares of Intercept common stock for US$19.00 per share in cash. The purchase price represents a premium of 82% to Intercept's closing stock price on September 25, 2023.



Alfasigma is paying only 2.2 times forward revenue for Intercept. This is one of the lowest acquisition multiples for a commercial company in some time.

Source: https://www.reuters.com/markets/deals/schott-pharma-debuts-frankfurt-stock-exchange-2023-09-28/

Azurity Pharmaceuticals Acquires Slayback Pharma

WOBURN, MA, September 27, 2023-- Azurity Pharmaceuticals, Inc. ("Azurity") is pleased to announce the closing of its acquisition of Slayback Pharma LLC ("Slayback") today from existing investors including KKR, a leading global investment firm, and Everstone Capital. Slayback is now a wholly-owned subsidiary of Azurity.

The acquisition brings together companies with complementary strengths, enhancing Azurity's ability to realize its purpose of Serving Overlooked Patients. The combined development portfolios are expected to yield a significant number of new medicine launches over the coming years.

Azurity leverages its integrated capabilities and vast partner network to continually expand its broad commercial product portfolio and robust pipeline. The company's patient-centric approach is evident in its diverse array of products catering to various medical needs, including cardiovascular, central nervous system, endocrinological, gastrointestinal, anti-infectives and oncology. Many of Azurity's medicines are dose-form innovations for patients with needs that are not met by other commercially available therapies.

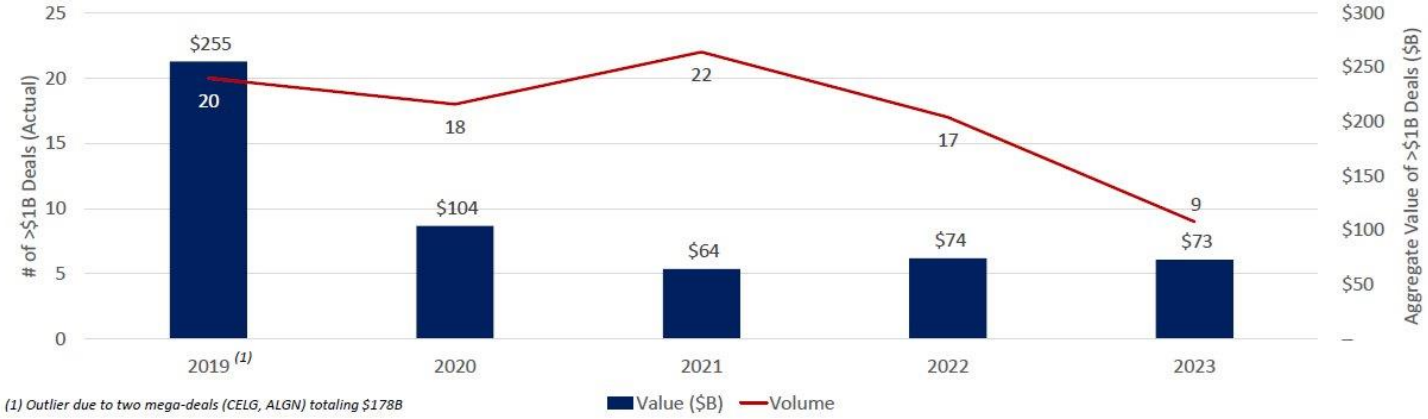
"I am delighted to announce this combination and the increased potential it brings to do more for overlooked patients," said Richard Blackburn, CEO of Azurity. "The complementary expertise of the two companies in developing innovative dose forms will result in a strong pipeline of new medicines to meet the needs of patients. We will bring the commercial expertise of Azurity to Slayback's pipeline and look forward to introducing an even wider range of dose-forms and formulations to meet a broader set of patient needs."

"The combination of Slayback and Azurity is a union of highly complementary capabilities: Azurity's innovative commercial acumen and Slayback's exceptional R&D platform. I am proud of Slayback's team, our track record of developing complex products with unmatched speed at scale, and the rich history we have built together. I am delighted to join forces with Azurity to help forge a combined entity that is truly one of a kind" added Ajay Singh, Founder and CEO of Slayback.

Source: https://azurity.com/azurity-pharmaceuticals-acquires-slayback-pharma/

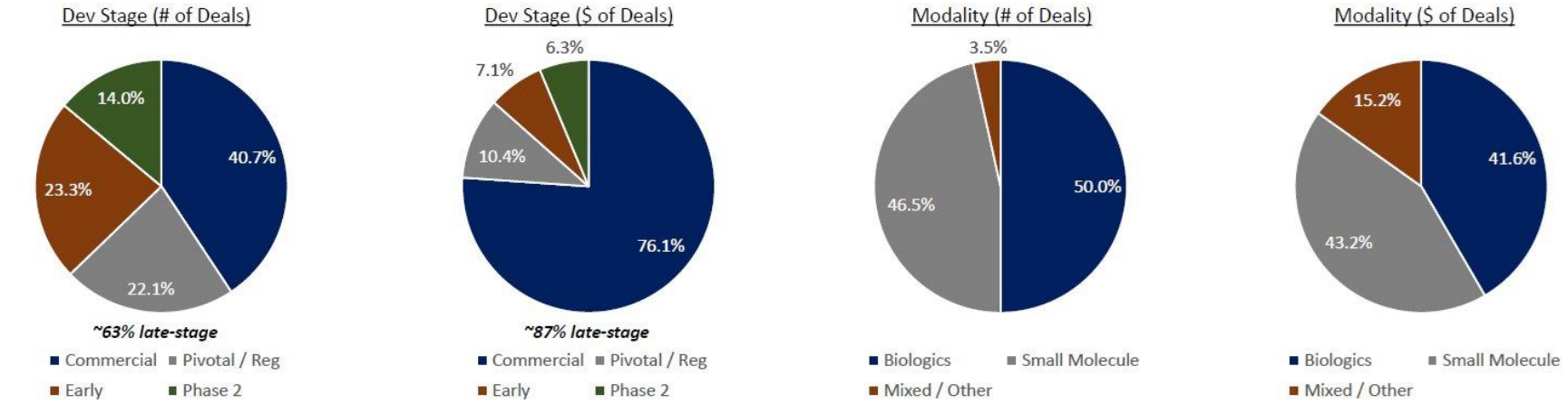
Andrew Pannu: M&A Since 2019 Is Largely Late Stage

YoY Deal Volume & Value (2019 – Present)



(1) Outlier due to two mega-deals (CELG, ALGN) totaling $178B

Cumulative % of Deals by Development Stage & Modality of Key Asset(s) (2019 – Present)



Andrew Pannu @andrewpannu

Note: 2023 data through 9/22/2023; "Mixed / Other" refers to ABBV / ALGN as Botox is a biologic, but remaining key assets were small molecule & Vectura Group deals, as it was more technology-based

Andrew Pannu:

"We've seen a noticeable dip in >$1B deals this year, although deal value is in-line (~$75B) with the past few years The majority (~63%) of deals have been for companies with approved or pivotal / registrational stage assets and the vast majority (~87%) of $ have been allocated here.

This makes sense given pharma's recurring need to replace at-risk LOE revenue, which is particularly pronounced over the next few years."

Sources: https://twitter.com/andrewpannu and https://andrewpannu.com/

Andrew Pannu: Upcoming LOE's Relevant to M&A

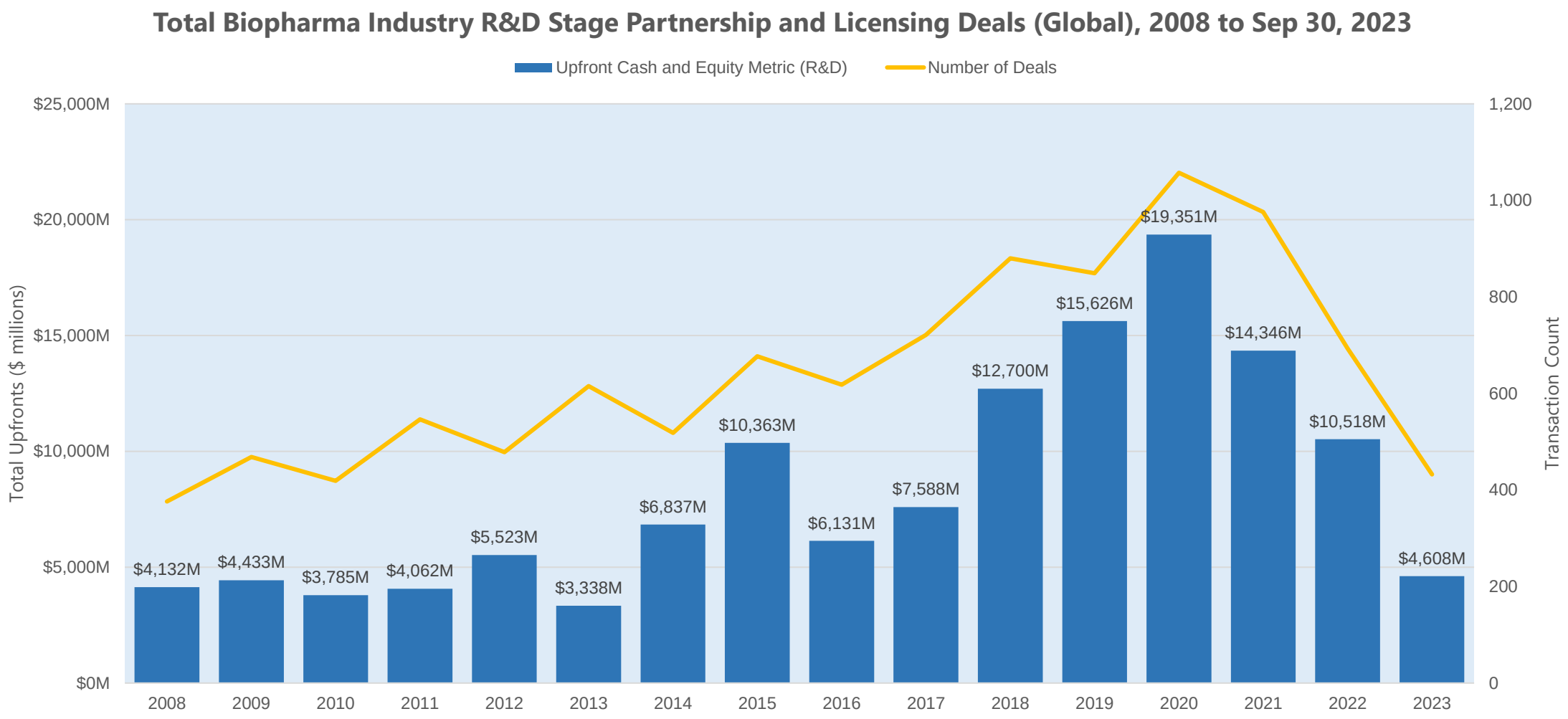
Notable LOEs through 2028

2023		2024		2025		2026		2027		2028	
Company	Product ('22 Sales)	Company	Product ('23 Sales)	Company	Product ('24 Sales)	Company	Product ('25 Sales)	Company	Product ('26 Sales)	Company	Product ('27 Sales)
abbvie	Humira ($21B)	REGENERON	Eylea ($10B)	AstraZeneca	Soliris ($2.7B)	NOVARTIS	Entresto ($7B)	Pfizer / Lilly	Eliquis ($15B)	MERCK	Keytruda ($30B)
Johnson & Johnson	Stelara ($10B)	AstraZeneca	Brilinta ($1.4B)	Bristol Myers Squibb	Yervoy ($3B)	EXELIXIS / IPSEN	Cabometyx ($1B)	abbvie / J&J	Imbruvica ($12B)	Bristol Myers Squibb	Opdivo ($13B)
Jazz Pharmaceuticals	Xyrem ($1B)	J&J / BAYER	Xarelto ($3B)	Pfizer	Xeljanz ($2B)	Bristol Myers Squibb	Pomalyst ($2.5B)	Pfizer	Ibrance ($9B)	AMGEN	Otezla ($3B)
Biogen	Tysabri ($1.9B)	novo nordisk	Victoza ($1.3B)	AMGEN	Prolia / Xjeva ($6B)	MERCK	Januvia / Janumet ($1B)	Lilly	Trulicity ($8B)	GSK	Tivicay ($4.5B)
sunovion	Latuda ($2B)					Roche	Perjeta ($5.5B)				
NOVARTIS	Gilenya ($1.6B)										
Takeda	Vyvanse ($3.4B)										
Total 'At-Risk' Revenue:	**~$41B**		**~$16B**		**~$14B**		**~$17B**		**~$44B**		**~$50B**

Andrew Pannu @andrewpannu

Sources: https://twitter.com/andrewpannu and https://andrewpannu.com/

Biopharma Licensing Volume Way Down in 2023



Source: DealForma

Industry News

FDA Rolls Out Long-Awaited Proposal to Overhaul Diagnostics Regulation

Lia DeGroot, *Endpoints News*, Sep 29, 2023 (excerpt)

The FDA on Friday unveiled a long-awaited proposed rule that aims to overhaul how the agency regulates diagnostic tests, bringing thousands of new tests under its purview.

The 83-page proposed rule makes explicit that in vitro diagnostics would be regulated as medical devices in the eyes of the FDA, and it would phase out its enforcement discretion approach for laboratory-developed tests (LDTs) over a period of four years. The rule fulfills FDA officials' commitments in recent months to pursue rulemaking to overhaul the agency's framework for regulating diagnostic tests in the absence of congressional action.

Lawmakers on the Hill have spent years attempting to solidify this authority for the FDA, but they have failed to pass legislation. The bill at issue is the Verifying Accurate, Leading-edge IVCT Development (VALID) Act, which would establish a risk-based regulatory framework for LDTs and create a user fee program for in vitro diagnostics.

Cathy McMorris Rodgers, chair of the House Energy and Commerce Committee, lambasted the FDA's proposed rule, saying it goes too far and will stifle innovation."

In order to strike the appropriate balance between adequate protections of public health and facilitating innovation, the FDA should rescind this rule and allow Congress—the people's voice—to consider the matter," she said in a statement.

The medical technology trade group AdvaMed said in comments Friday that it supports the establishment of a risk-based regulatory framework for in vitro clinical tests and said it is evaluating the proposed rule.

Source: https://endpts.com/fda-rolls-out-long-awaited-proposal-to-overhaul-diagnostics-regulation/

Without the Right Protections, We Might Say Goodbye To Our Biotech Innovation Sector

Frank Watanabe, Editorial, *The Hill*, Sep 29, 2023 (excerpt)

The United States lost its once-dominant position in semiconductor research and manufacturing thanks largely to shortsighted policy decisions. Thankfully, Congress, rightfully alarmed over the potential economic and national security implications, passed last year's bipartisan CHIPS Act — which invested $52 billion in domestic semiconductor research and manufacturing — to regain a foothold.

And yet, when it comes to our currently world-leading biotechnology industry, our leaders are repeating many of the same mistakes that ceded our leadership in semiconductors. They're creating an inhospitable policy environment that may well lead to the United States losing our preeminent position in that field as well. America's biotechnology sector is the envy of the world, at least for the time being. It develops about two-thirds of all new medicines invented worldwide.

U.S.-invented COVID vaccines helped end the pandemic, and important new applications of the mRNA technology behind those vaccines are on the horizon. Innovations in oncology have driven cancer death rates down by 33 percent — saving an estimated 3.8 million lives. And we're on the verge of important breakthroughs with revolutionary new medicines that have been shown to slow the progression of Alzheimer's disease. Medical advances have been so swift and dramatic that some scientists are calling our era a "golden age for medicine."

But we can't assume that U.S. leadership in biotechnology will endure. In fact, we weren't always leaders in the field. As recently as the late 1970s, European drug firms dominated the industry, introducing twice as many new drugs globally as U.S. firms. But an inhospitable policy environment in Europe, including intensive drug price controls, heavy-handed drug price negotiation tactics, regulations limiting biotechnology research, and limitations on mergers, undermined European competitiveness in biopharmaceuticals, allowing the United States to assume a global leadership position.

Unfortunately, the United States appears to be moving toward repeating many of the same policy mistakes that destroyed Europe's innovation ecosystem. Bad policy choices could weaken incentives to innovate, allowing nations like China to overtake us. We need to reverse course at once.

Much of the innovation that happens in the biotechnology sector starts with small, emerging companies. For example, so far this year, 65 percent of new medicines approved by the FDA have originated at small companies. These companies are powerhouses of innovation and often work closely with larger companies in the later stages of drug development.

Frank Watanabe is president and CEO of Arcutis Biotherapeutics. He is a BIO board member. He was a commissioned officer in the U.S. Navy Reserves for 25 years.

Source: https://thehill.com/opinion/congress-blog/4230691-without-the-right-ip-protections-we-might-say-goodbye-to-our-biotech-innovation-sector/

Pfizer Chief, Visiting Boston, Sees ‘Scientific Renaissance’ Over Coming Decade

Robert Weisman, *Boston Globe*, Sep 27, 2023 (excerpt)

Rapid advances in biology and technology will combine with the growing health needs of an aging population to fuel a “scientific renaissance” over the coming decade, the chief executive at drug giant Pfizer told Boston business and civic leaders Tuesday.

“Those two [trends], when they come together, will produce solutions that were impossible to find before,” helping to treat long-intractable diseases such as Alzheimer’s and cancer, Pfizer chief executive Albert Bourla said at a downtown luncheon hosted by Boston College’s Chief Executives Club.

Bourla, a native of Greece, told the crowd of about 150 people that he was broadly hopeful about therapeutic breakthroughs and the potential for artificial intelligence to accelerate every biopharma process from drug discovery to identifying patients to enroll in clinical trials.

“Overall, I’m very optimistic because no one follows a pessimist, no one,” Bourla said in a genial conversation moderated by Karen S. Lynch, the president and chief executive of CVS Health.

But he also warned that excessive government interventions to regulate drug pricing or limit patent protection — letting cheaper generics onto the market sooner — could handcuff drug makers, drive away investors, and dampen innovation.

Albert Bourla
Pfizer CEO

Source: https://www.bostonglobe.com/2023/09/27/business/pfizer-chief-visiting-boston-sees-scientific-renaissance-over-coming-decade/

Planning for CEO Succession in Biotech

Smooth Transitions: Planning For CEO And Board Succession

Posted September 28th, 2023

by Ankit Mahadevia, in From The Trenches, Leadership

Nobody stays in a particular role forever. While change at the senior level can be disruptive, it doesn't have to be. Teams and boards can work together to ensure that transitions happen smoothly and support continuity of the mission. At Spero, we executed on a succession process when I decided to step down after a decade leading the company, as did our Chairman. In one thoughtfully planned process, we found a great successor for me as CEO, I replaced our Chairman who remained on the Board, and another Board member stepped up as Lead Director.

The planning phase of CEO succession is the most intensive if you're doing it right:

- Good process strengthens the outcome: When you and a subset of your Board have thought hard enough annually about the issue, there's a temptation to crystallize plans quickly instead of bringing a larger group along. Ultimately, a succession plan for a CEO requires the buy-in of the full Board. A rushed process may be fast on the front end, but likely not serve the candidate that ultimately steps up to the role. If you're doing it right, all of the necessary deliberation and communication required is a labor intensive process (as my colleagues on the Board can attest).
- Have the right external support: The right external advisor can help greatly. In my experience, an advisor's longitudinal experience and pattern recognition are their most important contributions to the process. Based on his ability to draw on a variety of prior situations, our advisor was instrumental in pushing our thinking, building out a robust process, and helping us avoid groupthink. Internal support also helps – we were lucky to have a strong senior HR leader who offered valuable perspective.
- Be deliberate even if you think you have the answer: We were also fortunate to have a strong internal succession candidate. If you have that luxury, it's tempting to short-circuit the planning process; our Nom and Gov Committee did a great job starting from first principles on what the company needed, and taking the time with our advisor to consider internal and external succession paths systematically. While our internal candidate ended up having right experience, EQ, values, and strategic vision for the company, his mandate was stronger since he emerged from a thorough competitive process. (The considerations for who is "right" for a company and how to assay this merits an entire blog post which we'll aim to tackle in a future post).

Timing matters: Once it's clear that a succession plan needs to be activated, setting a clear timeline is important. Efficiency quarantines against the risk that the process prematurely impacts team dynamics. Teammates at small companies are pretty good at sniffing out when "something's up." An extended period of unspoken uncertainty can be a distraction and impact team dynamics. In addition, in the public company setting, timely disclosure also requires sticking to clear timelines when you decide to put a succession plan in motion.

Source: https://lifescivc.com/2023/09/smooth-transitions-planning-for-ceo-and-board-succession/

Standing at the Precipice of a Biotech Renaissance – the Confluence of AI and SynBio

Eleanor Garth, *Longevity Technology*, Sep 29, 2023 (excerpt)

Earlier this year, we reported on Integrated Biosciences, a biotech combining synthetic biology and machine learning to target aging, and its collaboration with researchers at the University of California Santa Barbara. They announced a drug discovery platform that enables precise control of the integrated stress response (ISR), a biological pathway that is activated by cells in response to a wide variety of pathological and aging-associated conditions.

This platform, which was featured on the cover of Cell Systems, triggers the ISR virtually using light and reveals how the accumulation of stress over time shifts a cell's reaction from adaptation to apoptosis (programmed cell death).

Wilson begins by acknowledging here that biological aging ranks among one of the most complex processes conceivable.

"It is influenced by genetic, environmental, and stochastic factors and involves a variety of 'pillars' that interact in unknown ways," he explains adding at the same time, biology has become such a data-rich science that machine models informed by this data are really the best tools for predicting outcomes.

Wilson describes the merging of AI and SynBio is a narrative of convergence – two of the most transformative technologies of our age coming together.

"This synergy heralds a new era in biotechnology, where computational might intersects with the boundless potential of biology, driving innovations at a pace previously unimaginable."

Integrated Biosciences is realizing the application of this convergence.

"We have a variety of lead compounds, borne from this synthesis of AI-driven insights and SynBio platforms, that we are preparing for IND-enabling studies," explains Wilson. "Our aim isn't just to drive innovation in isolation – we're actively looking out for strategic partnerships with other pioneering biotech companies and VC firms." Wilson adds that collaborative efforts like these can amplify the impact of discoveries, hastening their transition from the lab to real-world applications.

Source: https://longevity.technology/news/standing-at-the-precipice-of-a-biotech-renaissance-the-confluence-of-ai-and-synbio/

Shares of Biotech Startup Structure Therapeutics Surge More Than 30% on Promising Obesity Pill Data

Annika Kim Constantino, *CNBC*, Sep 29, 2023 (excerpt)

Shares of Structure Therapeutics rose more than 30% on Friday after the biotech startup's experimental obesity pill succeeded in a small early-stage trial.

The once-daily drug helped overweight or obese participants reduce up to 10 pounds of weight on average after four weeks of treatment, according to a release from the company. Structure said it plans to test its pill in two longer midstage trials as a treatment for diabetes and obesity.

Structure's pill is part of the same class of drugs as Novo Nordisk's blockbuster diabetes drug Ozempic and weight loss counterpart Wegovy.

Those treatments, known as GLP-1s, have soared in popularity this year due to their ability to help patients lose unwanted pounds. GLP-1s mimic a hormone produced in the gut to suppress a person's appetite.

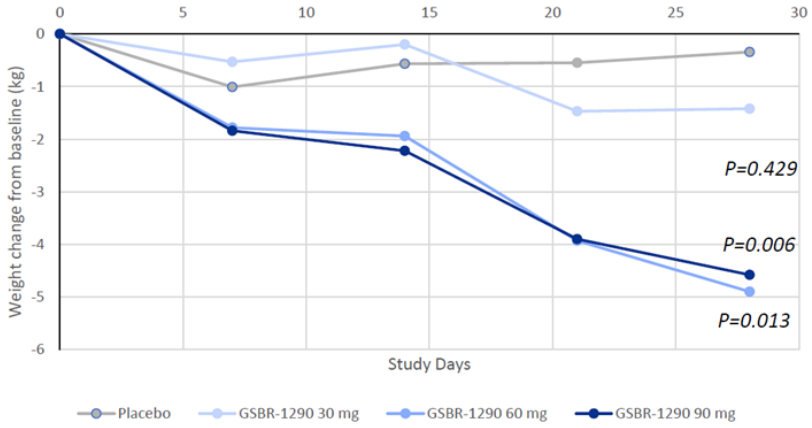
Source: https://www.cnbc.com/2023/09/29/obesity-pill-data-boosts-structure-therapeutics-shares.html

4.9% Weight Loss at 28 Days with GSBR-1290

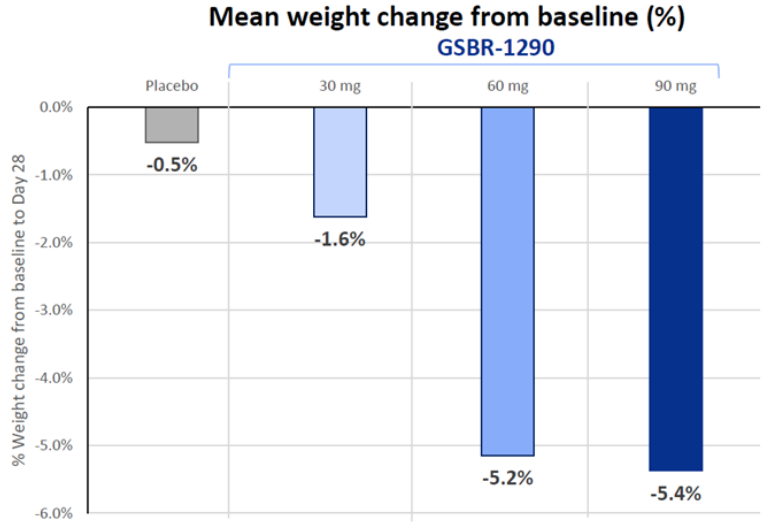
GSBR-1290 Phase 1b MAD study: Efficacy-Clinical activity

Positive signs of clinical activity at Day 28 with once-a-day dosing of GSBR-1290

Mean weight change from baseline (kg)



Mean weight change from baseline (%)



- Changes in body weight (BW) observed at early time points (first week)
- **Statistically significant reductions in BW (up to 4.9% placebo-adjusted) with QD dosing**

	Placebo	GSBR-1290 30 mg	GSBR-1290 60 mg	GSBR-1290 90 mg
% Change in BW placebo-adjusted	-	**-1.1%**	**-4.6%**	**-4.9%**
90% CI	-	-3.8 to 1.7	-6.6 to -2.7	-7.8 to -1.9
P-value vs placebo*	-	0.494	0.002	0.013

** Exploratory end point. t test*

STRUCTURE THERAPEUTICS

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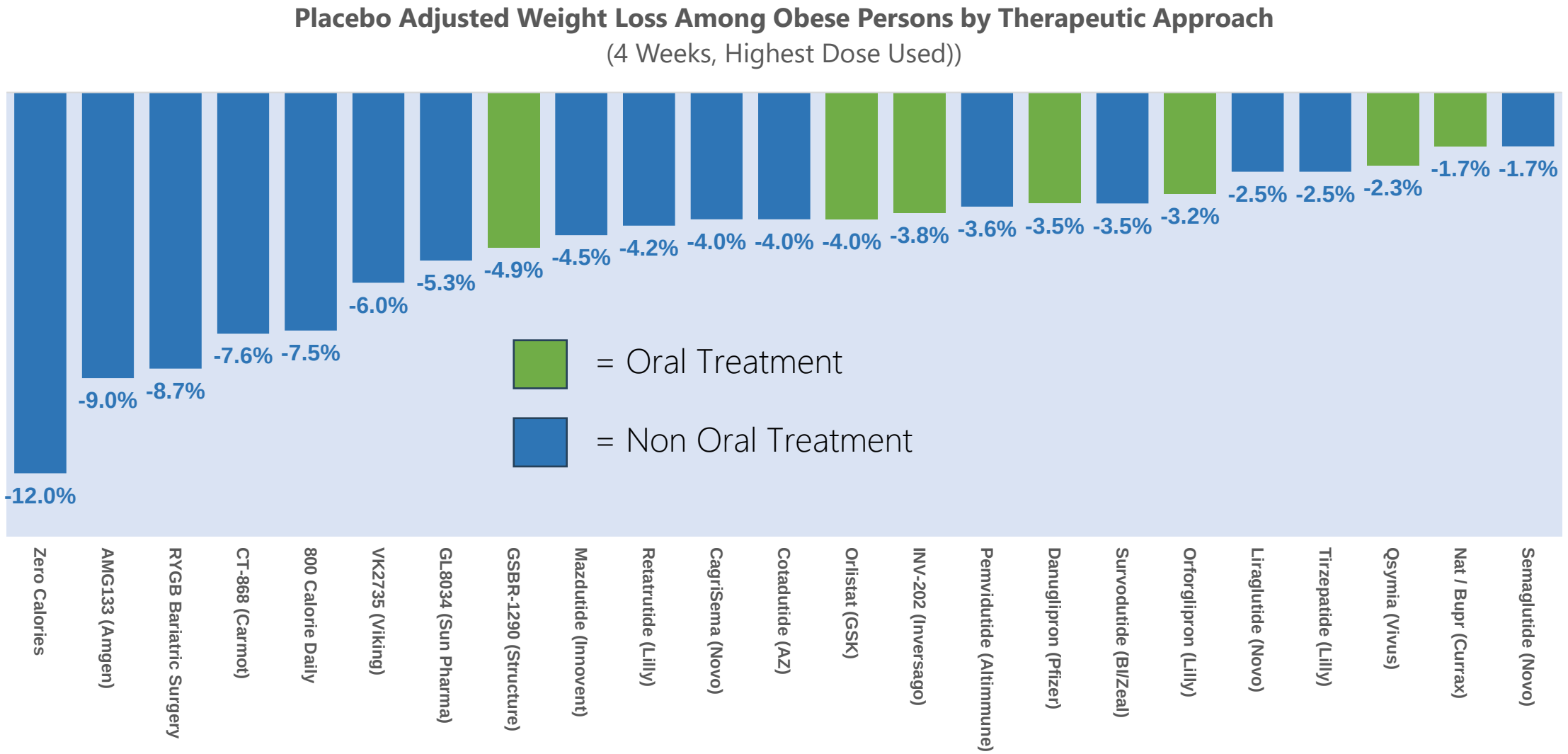
The 90mg dose was associated with a 50% vomiting and diarrhea rate but there were no treatment discontinuations.

Similar AE rates were seen at 28 days with Lilly's drug orforglipron.

Source: Structure Therapeutics, Sep 2023 data presentation.

Structure's GSBR-1290 Weight Loss Is The Most Impressive 4-Week Weight Loss Seen to Date With an Oral Treatment



Source: Stifel analysis.

The Brain Cells Linked to Protection Against Dementia

Sara Reardon, *Nature*, Sep 28, 2023 (excerpt)

Scientists have identified two types of brain cell linked to a reduced risk of dementia in older people — even those who have brain abnormalities that are hallmarks of Alzheimer's disease.

The finding could eventually lead to new ways to protect these cells before they die. The results were published in Cell on 28 September.

Neurobiologist Hansruedi Mathys at the University of Pittsburgh School of Medicine in Pennsylvania and neuroscientist Li-Huei Tsai and computer scientist Manolis Kellis at the Massachusetts Institute of Technology in Cambridge and their colleagues decided to investigate this disconnect. To do so, they used data from a massive study that tracks cognitive and motor skills in thousands of people throughout old age. The researchers examined tissue samples from 427 brains from participants who had died. Some of those participants had dementia typical of advanced Alzheimer's disease, some had mild cognitive impairment and the remainder had no sign of impairment.

The researchers isolated cells from each participant's prefrontal cortex, the region involved in higher brain function. To classify the cells, they sequenced all the active genes in each one. This allowed them to create an atlas of the brain showing where the different cell types occur.

The scientists identified two key cell types that had a specific genetic marker. One had active genes coding for reelin, a protein associated with brain disorders such as schizophrenia, and the other had active genes that code for somatostatin, a hormone that regulates processes throughout the body.

People who had greater levels of cognitive impairment, the researchers found, had relatively low numbers of these cells. Those who had no cognitive impairment had high numbers of the cells, even if they also had large amounts of amyloid in their brains that would typically denote Alzheimer's. This suggests that these cell types protect the brain against the disease's symptoms.

Source: https://www.nature.com/articles/d41586-023-03012-7

nature

https://doi.org/10.1038/s41586-023-06651-y

Accelerated Article Preview

Distinguishing features of Long COVID identified through immune profiling

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Accelerated Article Preview

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Jon Klein, Jamie Wood, Jillian Jaycox, Rahul M. Dhodapkar, Peiwen Lu, Jeff R. Gehlhausen, Alexandra Tabachnikova, Kerrie Greene, Laura Tabacof, Amyn A. Malik, Valter Silva Monteiro, Julio Silva, Kathy Kamath, Minlu Zhang, Abhilash Dhal, Isabel M. Ott, Gabrielee Valle, Mario Peña-Hernandez, Tianyang Mao, Bornali Bhattacharjee, Takehiro Takahashi, Carolina Lucas, Eric Song, Dayna Mccarthy, Erica Breyman, Jenna Tosto-Mancuso, Yile Dai, Emily Perotti, Koray Akduman, Tiffany J. Tzeng, Lan Xu, Anna C. Geraghty, Michelle Monje, Inci Yildirim, John Shon, Ruslan Medzhitov, Denyse Lutchmansingh, Jennifer D. Possick, Naftali Kaminski, Saad B. Omer, Harlan M. Krumholz, Leying Guan, Charles S. Dela Cruz, David van Dijk, Aaron M. Ring, David Putrino & Akiko Iwasaki

Post-acute infection syndromes (PAIS) may develop after acute viral disease. Infection with SARS-CoV-2 can result in the development of a PAIS known as "Long COVID" (LC). Individuals with LC frequently report unremitting fatigue, post-exertional malaise, and a variety of cognitive and autonomic dysfunctions; however, the biological processes associated with the development and persistence of these symptoms are unclear. Here, 273 individuals with or without LC were enrolled in a cross-sectional study that included multi-dimensional immune phenotyping and unbiased machine learning methods to identify biological features associated with LC. Marked differences were noted in circulating myeloid and lymphocyte populations relative to matched controls, as well as evidence of exaggerated humoral responses directed against SARS-CoV-2 among participants with LC. Further, higher antibody responses directed against non-SARS-CoV-2 viral pathogens were observed among individuals with LC, particularly Epstein-Barr virus. Levels of soluble immune mediators and hormones varied among groups, with cortisol levels being lower among participants with LC. Integration of immune phenotyping data into unbiased machine learning models identified key features most strongly associated with LC status. Collectively, these findings may help guide future studies into the pathobiology of LC and aid in developing relevant biomarkers.

Source: https://www.nature.com/articles/s41586-023-06651-y

Distinct Immune, Hormone Responses Shed Light on Mysteries of Long COVID

Bill Hathaway, Yale News, Sep 25, 2023

People who have experienced brain fog, confusion, pain, and extreme fatigue for months or longer after being infected with the COVID-19 virus exhibit different immune and hormonal responses to the virus than those not diagnosed with long COVID, according to a new study by researchers at Yale School of Medicine and Icahn School of Medicine at Mount Sinai.

The discovery of these distinct responses can help scientists for the first time identify the causes — and potentially explore cures — for the often debilitating illness that has afflicted millions of people worldwide. An estimated 7.5% of people infected with the SARS-CoV-2 virus in the U.S. later suffer from long COVID.

"If you are a doctor doing routine lab work on these patients, you are not going to find these signals," said Akiko Iwasaki, Sterling Professor of Immunobiology at Yale and co-senior author of the paper.

The findings were published Sept. 25 in the journal Nature. For the study, researchers analyzed blood samples from 268 people who had either experienced long COVID symptoms for an average of one year; had been infected with COVID-19 but had fully recovered; or had no known prior infections. The researchers observed significant differences between the circulating antibodies and other immune system cells among those with long COVID and the other groups of patients.

Among those who had exhibited long COVID researchers also found increased circulation of antibodies that help the body fight non-COVID-19 viruses, particularly those known to defend against Epstein-Barr virus, a human herpesvirus that has been linked with many cancers. In addition, these patients had markedly lower levels of cortisol, a steroid hormone released by the adrenal glands in times of stress.

While these findings reveal key biological processes associated with long COVID, the complexity of individual responses means developing therapies to treat the ailment will be difficult, the authors say.

"There is no 'silver bullet' for treating long COVID, because it is an illness that infiltrates complex systems such as the immune and hormonal regulation," said co-senior author David Putrino, a professor of rehabilitation and human performance at Icahn Mount Sinai and director of the Cohen Center for Recovery From Complex Chronic Illness.

The new insights, however, provide important clues that may help in developing new diagnostics and therapies, Iwasaki said.

"Once we have more information on these signals, we can start to think about designing the right trials to treat this condition," she said.

Source: https://news.yale.edu/2023/09/25/distinct-immune-hormone-responses-shed-light-mysteries-long-covid

Shionogi Drug Effective in Preventing Long Covid

OSAKA, Japan, September 19, 2023 - Shionogi & Co., Ltd. (Head Office: Osaka, Japan; Chief Executive Officer: Isao Teshirogi, Ph.D.; hereafter "Shionogi") will present two late-breaking posters at the European Scientific Working Group on Influenza and other Respiratory Viruses' (ESWI), 9th Influenza Conference, highlighting data suggesting the potential of its investigational oral antiviral ensitrelvir on symptoms associated with long COVID and in high-risk COVID-19 hospitalized patients with significant co-morbidities who did not respond to first-line treatment with remdesivir.

Ensitrelvir is an investigational oral antiviral that suppresses the replication of SARS-CoV-2 by selectively inhibiting the viral 3CL protease. Known as Xocova® in Japan, ensitrelvir received emergency regulatory approval from the Ministry of Health, Labour and Welfare (MHLW) for the treatment of SARS-CoV-2 infection in November 2022. It remains an investigational drug outside Japan. In April 2023, ensitrelvir was granted Fast Track designation by the U.S. Food and Drug Administration.

Shionogi will present a new exploratory analysis of the Phase 3 part of the pivotal SCORPIO-SR trial (Phase 2/3 study) conducted in Japan, South Korea and Vietnam, which shows that ensitrelvir may reduce the risk of a number of persistent and new late-onset symptoms associated with long COVID over one year. Long COVID was analyzed based on a patient-reported questionnaire at three months, six months and one year from the first date of treatment. In the study, long COVID was defined by patient reports of 'not having returned to pre-COVID health' and having at least one (mild or more severe) symptom out of 27 possible symptoms.

Ensitrelvir 125 mg and 250 mg showed a numerical relative risk reduction (25% and 26% respectively) versus the placebo group for 27 symptoms at one year. A similar trend in risk reduction was observed at three and six months. In addition, subgroup analyses found that greater risk reduction was observed in patients with BMI ≥25 kg/m2 and in patients with a median or higher symptom score at the start of treatment. The results of this exploratory analysis suggest that early treatment of COVID-19 with ensitrelvir may reduce the risk of a number of persistent and new late-onset symptoms associated with long COVID, but further confirmatory studies are needed.1

Shionogi has previously reported that the proportion of patients who experienced long COVID at six months with ensitrelvir was lower than in the placebo group using a different method of analysis of ongoing symptoms.

Long COVID is an often-debilitating illness that affects between 10-20% of people who get COVID-19. At least 65 million individuals worldwide are estimated to have long COVID, with cases increasing daily. More than 200 symptoms have been identified with effects on multiple organ systems.

Experts believe it is plausible that antivirals could prevent or reduce the risk of long COVID, but to date, no drug has been conclusively shown to reduce the risk of long COVID.

Source: https://www.shionogi.com/global/en/news/2023/9/20230919.html, https://www.shionogi.com/global/en/investors/ir-library/presentation-materials.html

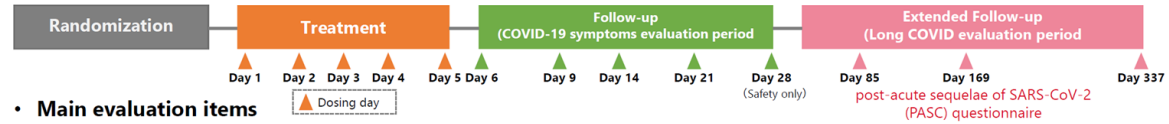
Effect of Ensitrelvir on Long COVID in Patients with Mild-to-Moderate COVID-19: A Post-Hoc Analysis of the Phase 3 SCORPIO-SR Study

Takeki Uehara / D.V.M., Ph.D. / Corporate Officer, Senior Vice President,
Drug Development and Regulatory Science Division, SHIONOGI&CO.,LTD.

SHIONOGI

Phase 3 part of Phase 2/3 trial Outline

- **Trial purpose**
  - To evaluate the efficacy and safety of ensitrelvir once-daily, 5 days oral treatment in patients with mild/moderate SARS-CoV-2 infection, aged 12-69 years regardless of SARS-CoV-2 vaccination, and risk factors for severe disease
- **Trial design**
  - Multicenter, randomized, double-blinded, placebo-controlled study conducted in Japan, South Korea and Vietnam from February to November in 2022



- **Main evaluation items**
  - Primary endpoint：Time to resolution[a] of five key Covid-19 symptoms
  - Key secondary endpoint：antiviral effect（viral RNA amount、virus titer)
  - Safety（Until the Day 28）
  - Exploratory endpoint: Presence of Long COVID symptoms evaluated by PASC questionnaire (27 symptoms)
    - Data up to Day 169 has already been reported at CROI 2023 in February 2023, and data up to Day 337 is the subject of this report

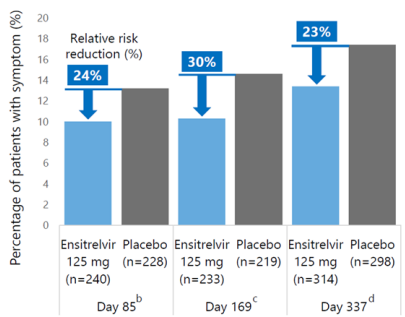
12 [a] Time to return to pre symptomatic state, defined as time to "recovery" in the trial protocol

SHIONOGI

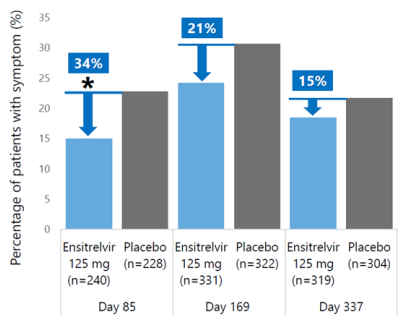
Proportion of Patients with Long COVID Symptoms and Effect on Long COVID Symptoms

Definition of Long COVID symptoms: At least one specified symptom self-judged as related to COVID-19

Percentage of patients with any of the 14 symptoms



Percentage of patients with any of the 4 neurological symptoms[a]



*P value of <0.05 using Fisher's exact test.

The proportion of patients with Long COVID symptoms in the ensitrelvir 125 mg was lower than that in the placebo group at all timepoints.

[a] Difficulty with concentration and thinking, difficulty reasoning and solving problems, memory loss, or insomnia.
[b] Patients who perceived any of the symptoms at both last observation in the follow-up period (e.g., Day 21) and Day 85.
[c] Patients who perceived any of the symptoms at both Day 85 and Day 169. [d] Patients who perceived any of the symptoms at both Day 169 and Day 337.

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Proportion of patients who did not return to usual (pre-COVID) health

Patients who answered "No" to the question "Have you returned to your usual (pre-COVID) health?".

	125 mg N = 379	Placebo N = 362
Day 85	7.5% (18/240)	11.8% (27/228)
Day 165	7.6% (25/331)	10.2% (33/322)
Day 337	6.0% (19/319)	8.2% (25/304)

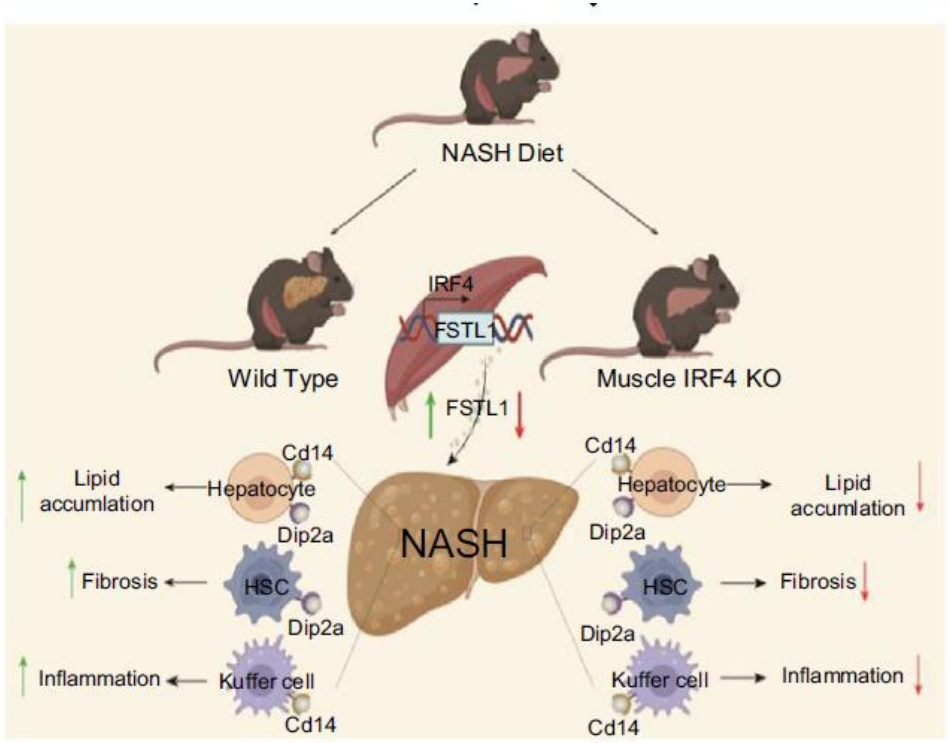
The proportion of patients not having returned to usual health in the ensitrelvir treatment group was lower than that in placebo group at all the timepoints.

Source: https://www.shionogi.com/global/en/news/2023/9/20230919.html, https://www.shionogi.com/global/en/investors/ir-library/presentation-materials.html

Metabolic Crosstalk Between Skeletal Muscle Cells and Liver Through IRF4-FSTL1 in Nonalcoholic Steatohepatitis

Guo S, et.al. *Nat Commun*. 2023 Sep 28;14(1):6047.

Inter-organ crosstalk has gained increasing attention in recent times; however, the underlying mechanisms remain unclear. In this study, we elucidate an endocrine pathway that is regulated by skeletal muscle interferon regulatory factor (IRF) 4, which manipulates liver pathology. Skeletal muscle specific IRF4 knockout (F4MKO) mice exhibited ameliorated hepatic steatosis, inflammation, and fibrosis, without changes in body weight, when put on a nonalcoholic steatohepatitis (NASH) diet. Proteomics analysis results suggested that follistatin-like protein 1 (FSTL1) may constitute a link between muscles and the liver. Dual luciferase assays showed that IRF4 can transcriptionally regulate FSTL1. Further, inducing FSTL1 expression in the muscles of F4MKO mice is sufficient to restore liver pathology. In addition, co-culture experiments confirmed that FSTL1 plays a distinct role in various liver cell types via different receptors. Finally, we observed that the serum FSTL1 level is positively correlated with NASH progression in humans. These data indicate a signaling pathway involving IRF4-FSTL1-DIP2A/CD14, that links skeletal muscle cells to the liver in the pathogenesis of NASH.



Source: https://pubmed.ncbi.nlm.nih.gov/37770480/

nature communications

Article

https://doi.org/10.1038/s41467-023-41683-y

IFNγ-Stat1 axis drives aging-associated loss of intestinal tissue homeostasis and regeneration

Received: 28 October 2021

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Published online: 30 September 2023

Check for updates

Omid Omrani[1,5], Anna Krepelova[1,2,3,5], Seyed Mohammad Mahdi Rasa[1], Dovydas Syrvinskas[1], Jing Lu[1], Francesco Annunziata[1], George Garside[1], Seerat Bajwa[1], Susanne Reinhardt[4], Lisa Adam[1], Sandra Käppel[1], Nadia Ducano[2,3], Daniela Donna[2,3], Alessandro Ori[1], Salvatore Oliviero[2,3], Karl Lenhard Rudolph[1] & Francesco Neri[1,2,3]

The influence of aging on intestinal stem cells and their niche can explain underlying causes for perturbation in their function observed during aging. Molecular mechanisms for such a decrease in the functionality of intestinal stem cells during aging remain largely undetermined. Using transcriptome-wide approaches, our study demonstrates that aging intestinal stem cells strongly upregulate antigen presenting pathway genes and over-express secretory lineage marker genes resulting in lineage skewed differentiation into the secretory lineage and strong upregulation of MHC class II antigens in the aged intestinal epithelium. Mechanistically, we identified an increase in proinflammatory cells in the *lamina propria* as the main source of elevated interferon gamma (IFNγ) in the aged intestine, that leads to the induction of Stat1 activity in intestinal stem cells thus priming the aberrant differentiation and elevated antigen presentation in epithelial cells. Of note, systemic inhibition of IFNγ-signaling completely reverses these aging phenotypes and reinstalls regenerative capacity of the aged intestinal epithelium.

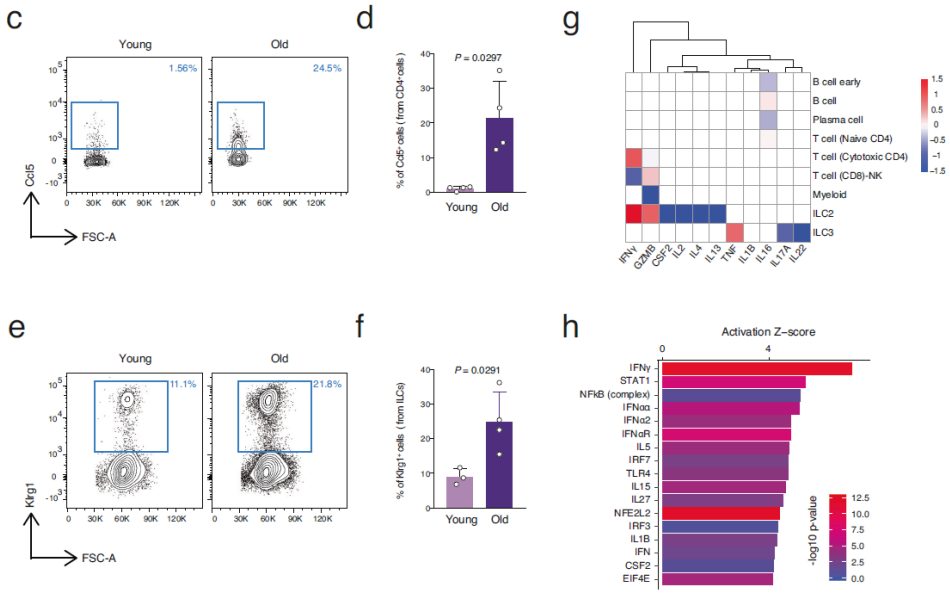


Fig. 4 | Aging lamina propria immune cell composition changes towards proinflammatory condition. c Representative FACS plots showing percentages of CCL5+ CD4 T (cytotoxic) cells in the indicated ages. d The bar chart shows the percentage of CCL5+ cells from CD4 T cells in the indicated ages. n = 4 mice per group were analyzed. Error bars represent the SD. P value was calculated by two-sided Welch's t test. e Representative FACS plots showing percentages of Klrg1+ ILC2s in the indicated ages. f The bar chart shows the percentage of Klrg1+ ILC2s in the indicated ages. n = 3 (young) and n = 4 (old) mice per group were analyzed. Error bars represent the SD. P value was calculated by two-sided Welch's t test. g Hierarchical clustering and heatmap of gene expression for identified cytokines in our scRNAseq datasets. h Upstream regulators associated with the DEGs from RNA-seq of intestinal crypts cells during aging. X axis shows the activation Z score of each upstream regulator, and color code shows enrichment P value (−log10). P value is calculated using the right-tailed Fisher Exact Test.

Source: https://www.nature.com/articles/s41467-023-41683-y

Update on Antimicrobial Resistance

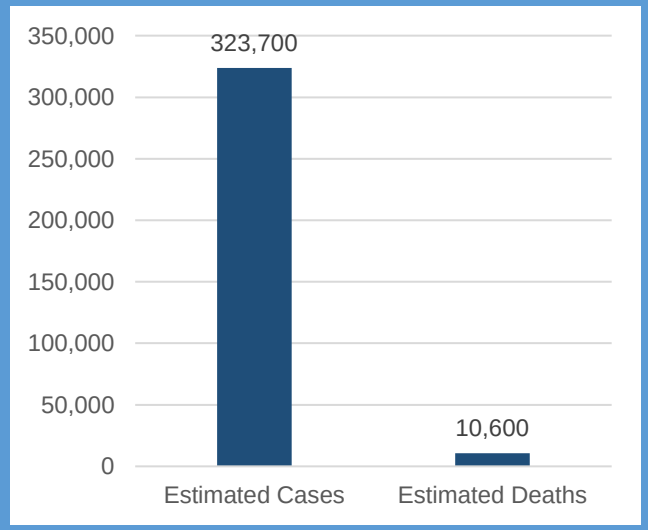
Antimicrobial Resistance Threat Level High

CDC (Sep 2023): "Antimicrobial resistance is an urgent global public health threat, killing at least 1.27 million people worldwide and associated with nearly 5 million deaths in 2019. In the U.S., more than 2.8 million antimicrobial-resistant infections occur each year."

Methicillin-resistant Staphylococcus aureus

Threat level: **Serious**

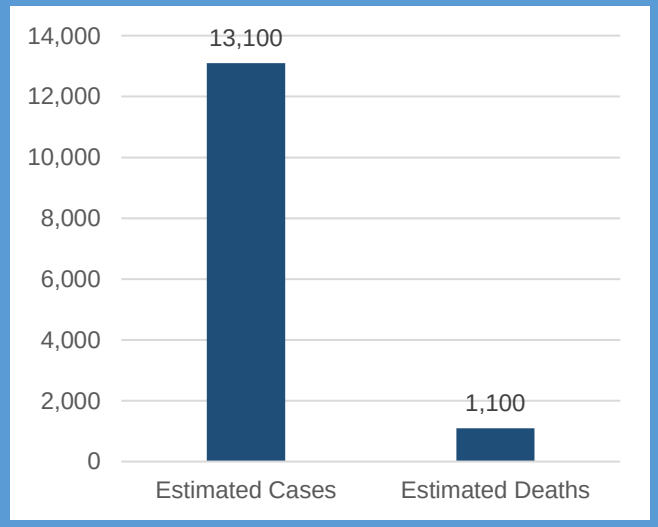
Healthcare Costs: **$1.7 B**



Carbapenem-resistant Enterobacter

Threat level: **Urgent**

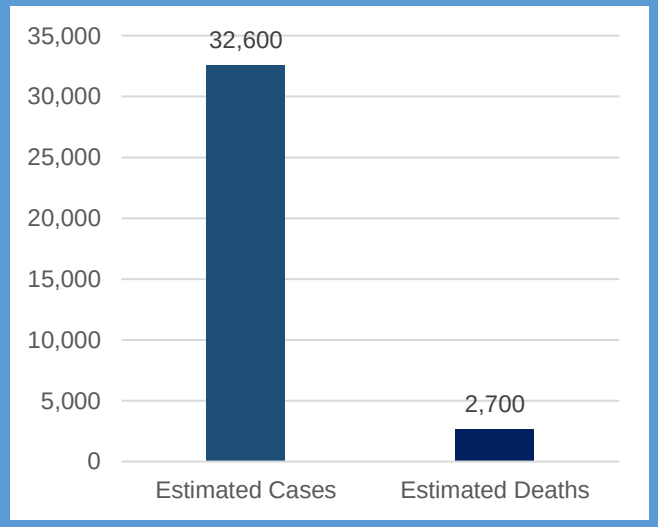
Healthcare Costs: **$130 M**



Multidrug-resistant Pseudomonas aeruginosa

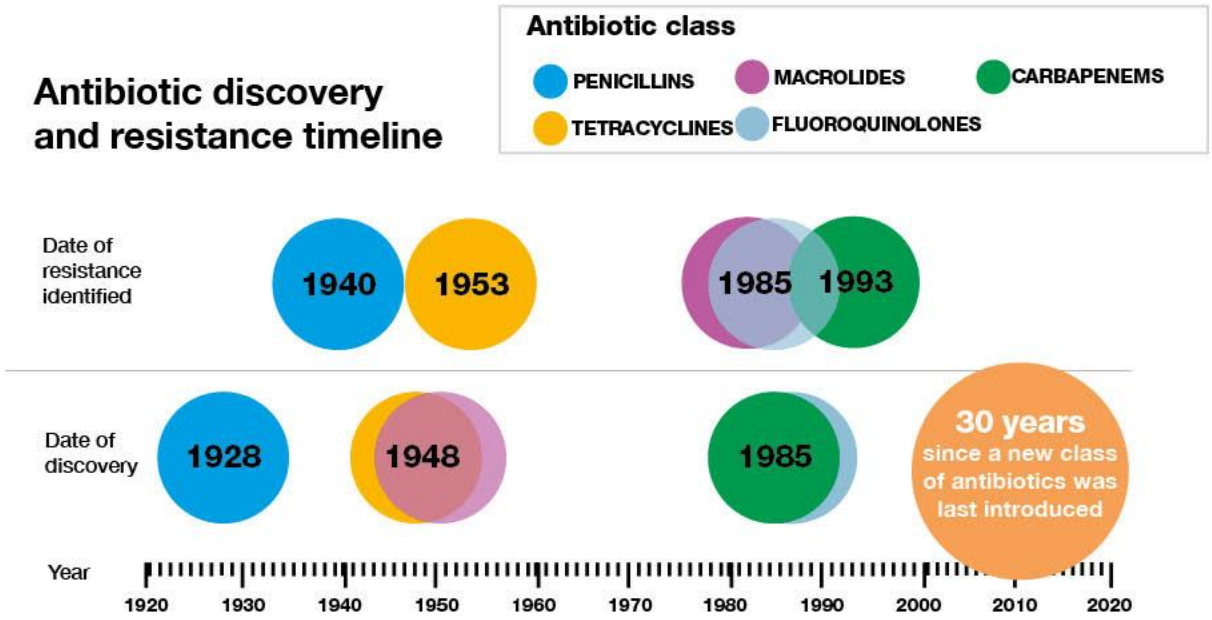
Threat level: **Serious**

Healthcare Costs: **$767 M**



Source: *Antibiotic Resistance Threats in the United States*, CDC,

Microbial Resistance Accelerating



Source: https://www.gov.uk/government/publications/health-matters-antimicrobial-resistance/health-matters-antimicrobial-resistance

The World Needs New Antibiotics. The Problem Is, No One Can Make Them Profitably.

New drugs to defeat 'superbug' bacteria aren't reaching patients

Dominique Mosbergen, *Wall Street Journal*, Sep 26, 2023 (excerpt)

The push for antibiotics to fight fast-evolving superbugs is snagging on a broken business model.

Six startups have won Food and Drug Administration approval for new antibiotics since 2017. All have filed for bankruptcy, been acquired or are shutting down. About 80% of the 300 scientists who worked at the companies have abandoned antibiotic development, according to Kevin Outterson, executive director of CARB-X, a government-funded group promoting research in the field.

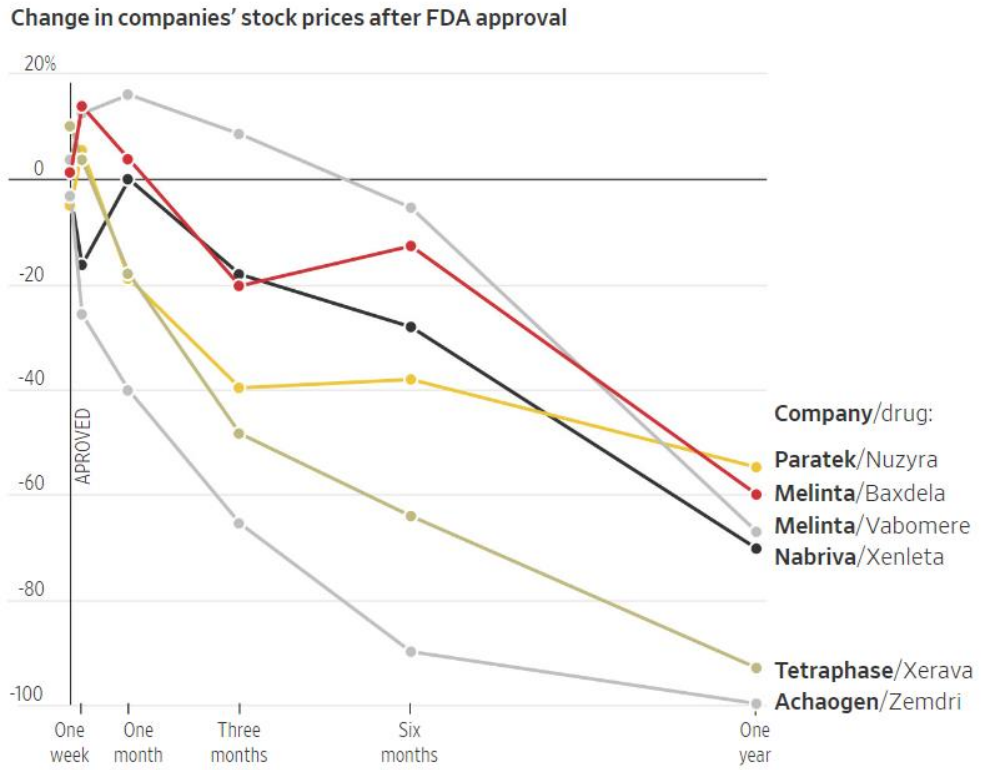
"These companies are supposed to be the winners, but every one of them is an unhappy story," Outterson said.

Nabriva Therapeutics terminated its 60 remaining employees this year and is seeking a buyer, four years after the FDA approved its antibiotic Xenleta for pneumonia. Nabriva priced a five-day treatment of Xenleta at over $1,000. Generic antibiotics to treat people who develop pneumonia outside of hospitals typically cost under $100. Fewer than 100 of the 800 hospitals Nabriva approached bought it.

"It was all driven by cost," Nabriva's former Chief Executive Officer Ted Schroeder said.

Unrealized Gains

Some companies that received FDA approval for antibiotics between 2017-2019 saw their stock prices slide.



Note: Performance on day of FDA approval based on change from the previous day. Performance for other dates based on change since approval date.
Source: Dow Jones Market Data; FactSet
Josh Ulick/THE WALL STREET JOURNAL

Source: https://www.wsj.com/tech/biotech/antibiotics-drug-development-business-fda-aa5b4f00

Sticking together makes bacteria nearly invincible

New treatments are trying to drive them apart

Economist, Sep 27, 2023 (excerpt)

Cohabitation brings big benefits. When biofilms grow large enough, they become hard for hostile parties to penetrate. Some estimates suggest these fortresses can make bacteria up to 1,000 times harder for antibiotics to dislodge. But what is a boon for the bacteria is the bane of many of the humans who must live alongside them. Figures from 2022 suggest that biofilms play a role in 60% of all human bacterial infections. They congregate on joint implants and clog up catheters. They colonise bed rails, light switches and incubators in hospitals. They infect open wounds, and produce the plaque between your teeth.

In 2017 Britain's National Biofilm Innovation Centre put the global economic burden of biofilms at over $3.9trn. That represents more than just health costs. Biofilms can corrode metals and gunk up infrastructure.

Despite the scale of the problem, it has drawn little attention. One reason is that biofilms are comparatively poorly understood. Several different species of bacteria can unite in a single biofilm, which makes it harder to create accurate models in a lab. All the same, progress is being made. A better understanding of biofilms is indicating ways to get rid of them.

No two biofilms are exactly alike. But they begin when a bacterium finds its way to a surface, often attracted by food. It secretes sticky compounds to attach itself and begins to divide. Within a couple of days—or a few hours, for the fastest-reproducing strains—a small colony of descendants has formed.

Rather than finding ways into the fortress, some are hoping to tear it down. In 2008 Steven Goodman, then at the University of Southern California, and his collaborator Lauren Bakaletz at Ohio State University, found what seemed to be two universal components of biofilms—standard-issue screws that could be loosened with the right tool. The screws in question are two proteins in a family known as dnabII (pronounced dna-b-2). They bind to places where strands of dna scaffolding cross. Remove them, and biofilm should collapse.

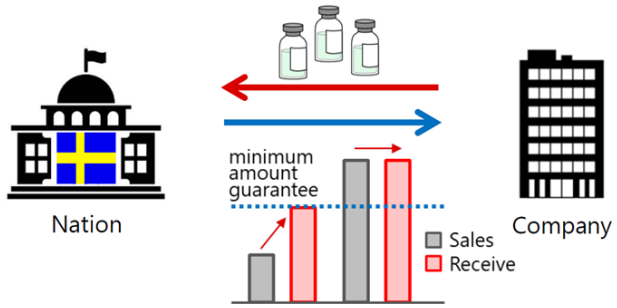
Source: https://www.economist.com/science-and-technology/2023/09/27/sticking-together-makes-bacteria-nearly-invincible

Innovation in Antibiotic Pricing: Fetroja Marketing in Europe

Cefiderocol: subscription-type reimbursement model

【UK model】
A system where the government pays the company a fixed amount of compensation regardless of the amount of antimicrobial drugs prescribed, and the government can obtain the antimicrobial drugs needed

【Swedish model】
A system where payment for a minimum amount is guaranteed, and if the amount supplied exceeds the minimum, revenue for that is also earned



subscription-type reimbursement model
- Adopted antimicrobial drugs
  - Fetcroja（cefiderocol）
  - ceftazidime/avibactam（Zavicefta: Avycaz）
- Subscription payment contract period is scheduled to start in April 2022

delinked incentive model
- Adopted antimicrobial drugs
  - Zerbaxa（ceftolozan-tazobactam）
  - Recarbrio（imipenem-cilastatin-relebactam）
  - Fetcroja（cefiderocol）
  - Vaborem（meropenem-vaborbactam）
  - Fosfomycin infectopharm（fosfomycin）

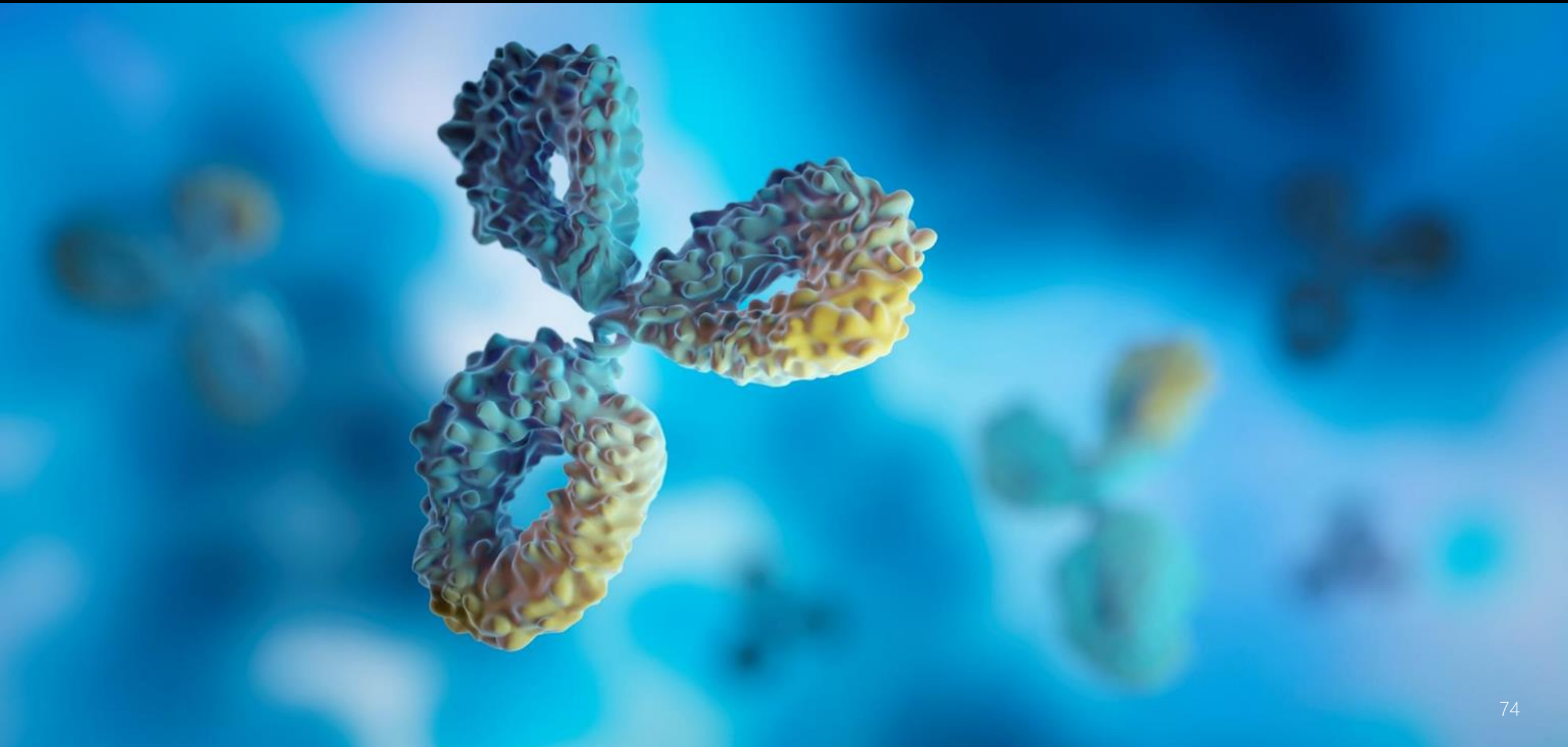
SHIONOGI 30

The UK government pays Shionogi a fee of $13mm a year for being able to access cefidorocol in the NHS. Physicians are incentivized this drug given that it is already paid for.

In Sweden a different model exists where a minimum payment is made to access the drug. If sales go above a certain level, additional payments would be made.

Source: Shionogi investor presentation, Feb 2021.

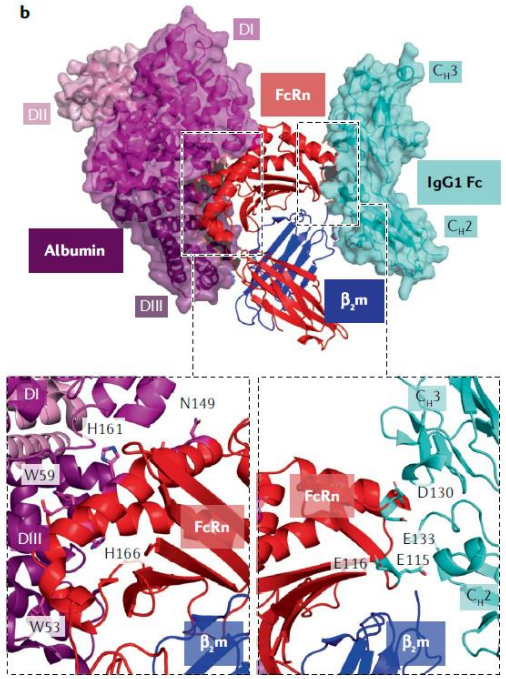
FcRn Update: Immunovant and Biohaven News



FcRn Binds IgG and Albumin via Distinct Pockets to Protect Them From Degradation

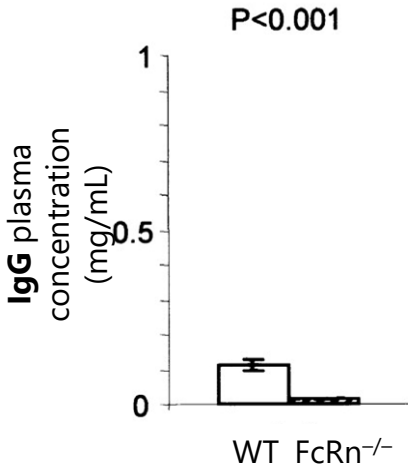
By preventing degradation of IgG antibodies, FcRn extends the half live of circulating antibodies, including pathological autoantibodies.

Key FcRn Binding Sites



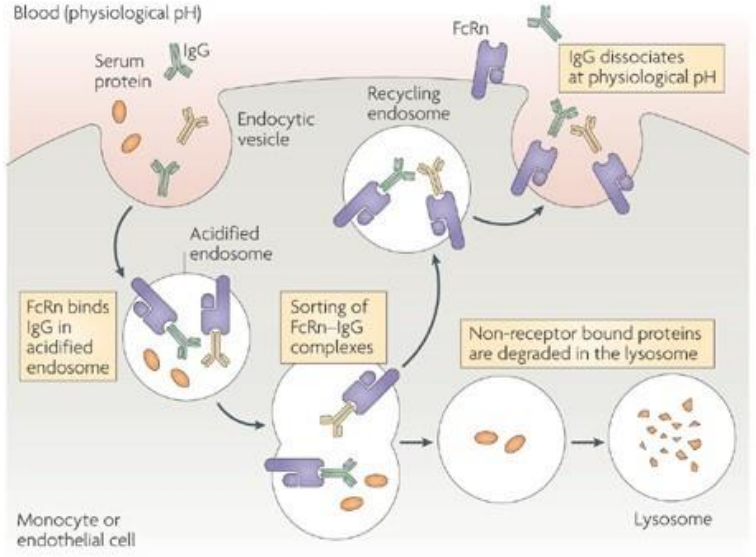
Pyzik et al., *Nat Reviews Immunology, 2023*

FcRn deficiency decreases albumin and IgG levels in the circulation



Chaudhury et al., *J Exp Med*, 2003

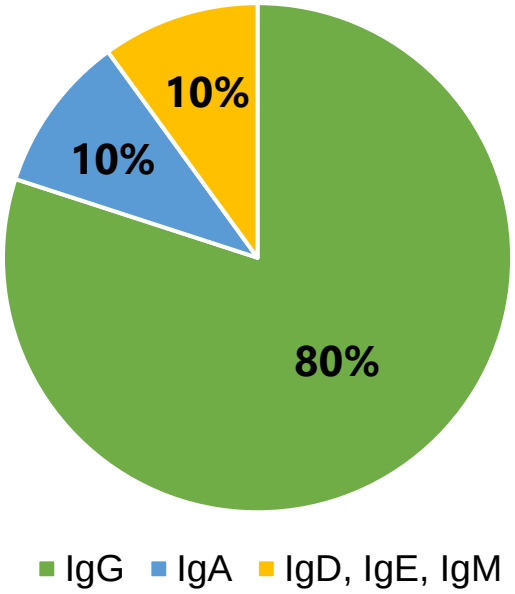
FcRn binds its ligands in endosomes, preventing degradation



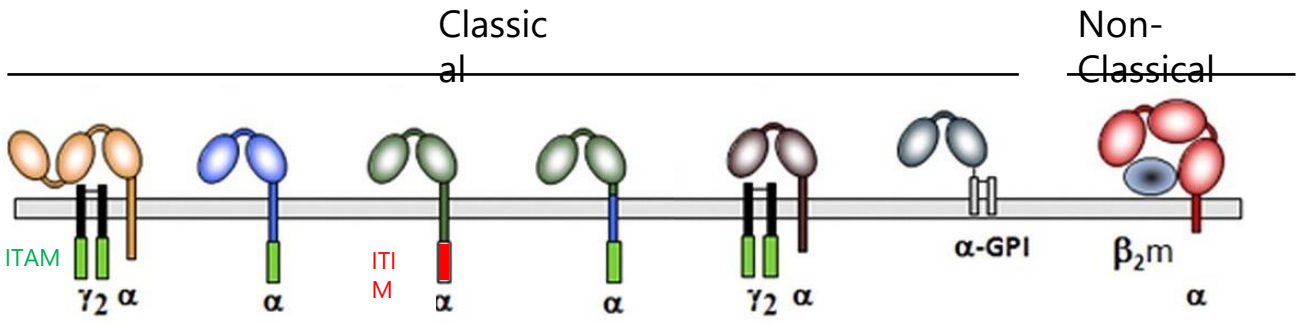
Roopenian et al., *Nature Reviews Immunology*, 2007

FcRn is One of a Class of 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

FcRn Receptor Preserves IgG by Transcytosis

FcRn extends the half-life of IgG and serum albumin by reducing lysosomal degradation in endothelial cells and bone-marrow derived cells. IgG, serum albumin and other serum proteins are continuously internalized through pinocytosis. Generally, serum proteins are transported from the endosomes to the lysosome, where they are degraded. The two most abundant serum proteins, IgG and serum albumin are bound by FcRn at the slightly acidic pH (<6.5) and recycled by transcytosis to the cell surface where they are released at the neutral pH (>7.0) of blood. In this way IgG and serum albumin avoids lysosomal degradation. This mechanism provides an explanation for the greater serum circulation half-life of IgG and serum albumin.

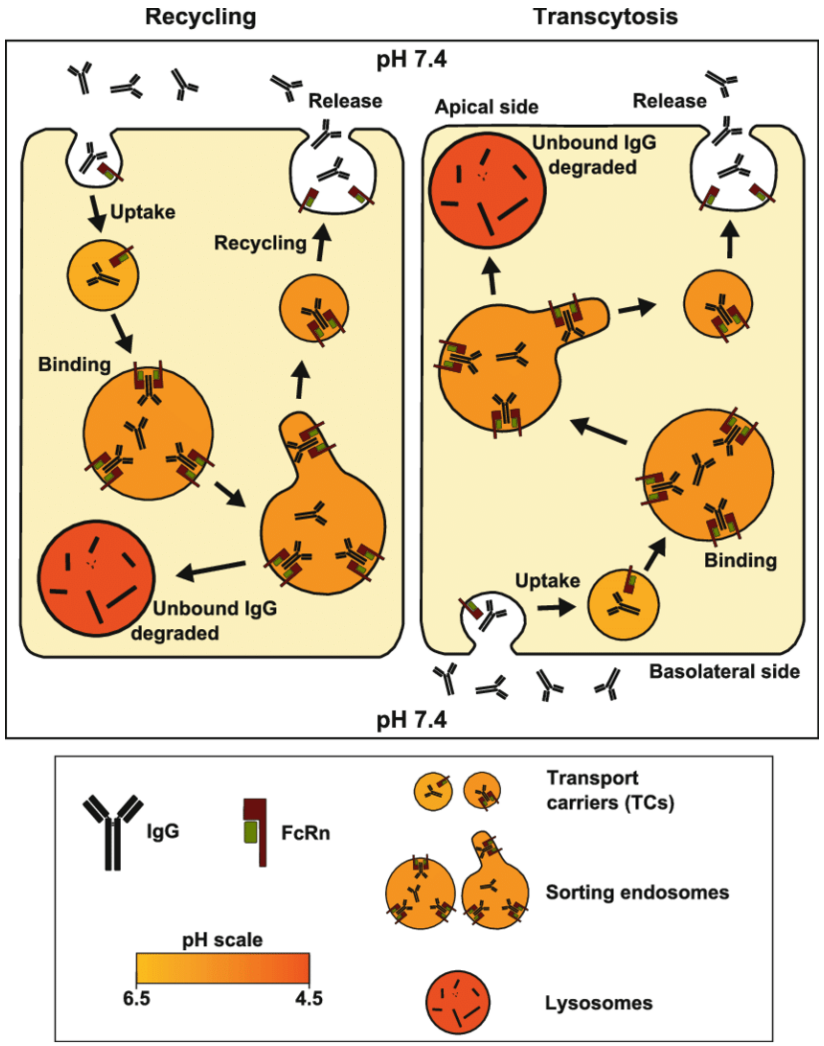


Chart source: Challa, Dilip & Velmurugan, Ramraj & Ober, Raimund & Sally Ward, E. (2014). FcRn: From Molecular Interactions to Regulation of IgG Pharmacokinetics and Functions. Current topics in microbiology and immunology. 382. 249-72.

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)  IgG4 mAb	pH 6.0: 0.02	MG	II or III	NCT04124965, NCT03971422, NCT03052751, 2016-002698-36	(101,102 103, 104)
		ITP	II or III	NCT02718716, NCT04224688, NCT04200456	
	pH 7.4: 0.03	CIDP	II	NCT04051944, NCT03861481	
			I	NCT02220153, NCT03859219	
Efgartigimod (ARGX-113; Argenx)  IgG1 Fc fragment (M252Y/S254T/ T256E/H433K/N434F)	pH 6.0: 14	MG	II or III	NCT03770403, NCT03669588, NCT02965573	(105, 106)
		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)  Aglycosylated IgG1 mAb	pH 6.0: 0.04	WAIHA	III	NCT04119050	(107, 108)
		HDFN	II	NCT03842189, NCT03755128	
		MG	II	NCT03896295, NCT03772587	
			I	NCT02828046	
	pH 7.4: 0.03				
IMVT-1401 (RVT-1401; Immunovant)  mAb	None available	MG	II	NCT03863080	(109)
		Graves' ophthalmopathy	II	NCT03922321, NCT03938545	
		WAIHA	II	NCT04253236	

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)  IgG4 mAb (S241P mutation)	pH 6.0: 1.19 pH 7.4: 0.87	Pemphigus (PV or PF) WAIHA	II	NCT03075904	(110, 111)
			II	NCT03075878, NCT04256148	
			I	NCT03643627	
ABY-039 (Alexion)  Bivalent antibody-mimetic	None available		I	NCT03502954	

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

Illustrative Relatively Common Diseases Associated with Auto-Antibodies

Disease	G8 Prevalence	Impact	Need
Grave's Disease	10,800,000	Moderately debilitating	20% of patients not responsive
Grave's Orbitopathy (sequellae of GD)	10,800,000	Moderately debilitating	20% of patients not responsive
Celiac Disease (subset)	8,800,000	Moderately debilitating	High need
Autoimmune thyroiditis (Hashimoto's)	5,900,000	Moderately debilitating	Little need
Fibromyalgia (subset)	5,300,000	Moderately debilitating	High need
Vitiligo	3,630,000	Moderately debilitating	High need
Inflammatory Bowel Disease	3,220,000	Moderately to highly debilitating	Some need
Autoimmune urticaria	2,500,000	Moderately debilitating	Some need
Autism (subset with FRAA)	2,440,000	Severely debilitating	High need
Deep Vein Thrombosis (subset)	2,362,500	Severely debilitating	Some need
Sjogren's Syndrome	1,680,000	Not debilitating for vast majority patients	Little need
Systemic Lupus Erythematosus	827,000	Severely Debilitating for many patients	High need
Lupus Neuropsychiatric	415,000	Debilitating	High need
ANCA Associated Vasculitis	366,240	Debilitating	Moderate need
IgA Nephropathy (subset)	360,000	Severely debilitating	High need
Sclerosis - CREST syndrome	197500	Moderately debilitating	High need
Antiphospholipid syndrome	197,000	Debilitating	High need
Myasthenia Gravis	185,000	Severely Debilitating	Moderate need
Immune Thrombocytopenic Purpura	128,000	Sometimes debilitating in adults	Moderate need
Autoimmune hepatitis	126,000	Can be debilitating	High need
Henoch-Schonlein purpura (HSP)	123,000	Not debilitating	Little need
CIDP (Chronic Immune Demyelinating Polyneuropathy)	120,000	Debilitating	Moderate need
Diabetes Type I	115,000	Debilitating	High need
Warm Autoimmune Hemolytic Anemia	114,250	Severely Debilitating	High need
Lupus Nephritis	105,000	Moderately to highly debilitating	High need

Source: Stifel Research

Illustrative Less Common Diseases Associated with Auto-Antibodies

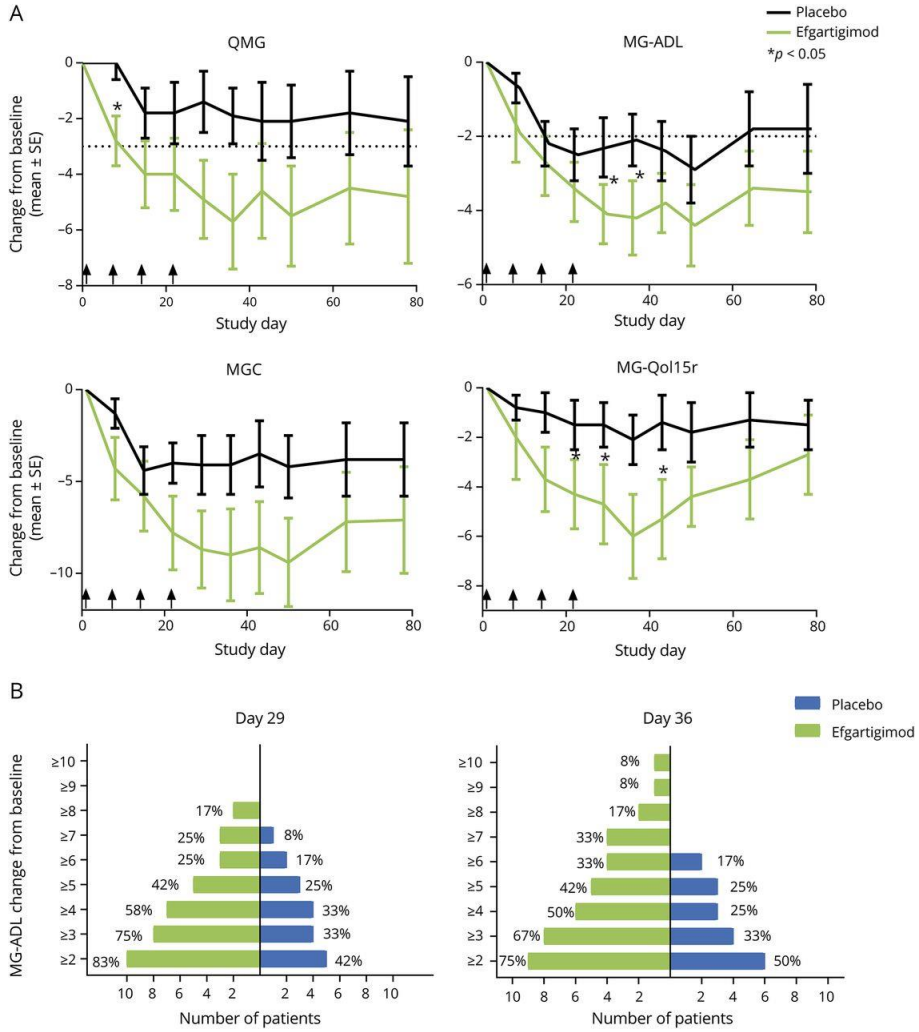
Disease	G8 Prevalence	Impact	Need
Pemphigus vulgaris	90,000	Debilitating	Moderate need
Herpes gestationis	85,000	Moderately debilitating	Moderate need
ALS	75,000	Severely Debilitating	High need
Fibrosing alveolitis	70,500	Severely debilitating	High need
Membranous Nephropathy	66,000	Debilitating	High need
Polymyositis (PM)	56,130	Debilitating	High need
Rheumatic fever	43,600	Not debilitating for vast majority patients	Little need
Erythema nodosum	25,200	Moderately debilitating	High need
Pemphigus Foliaceus	19,000	Moderately debilitating	Moderate need
Discoid lupus	18,000	Moderately debilitating	High need
Bullous Pemphigoid	14,000	Sometimes debilitating in adults	Moderate need
Neuromyelitis Optica (NMOSD)	13,000	Severely Debilitating	Moderate need
Autoimmune neutropenia	12,000	Sometimes debilitating in adults	High need
Guillain-Barré Syndrome	11,000	Debilitating	Moderate need
Dermatomyositis (DM)	9,400	Moderately debilitating	High need
Autoimmune pancreatitis	9,200	Not debilitating for vast majority patients	High need
Essential mixed cryoglobulinemia	9,000	Moderately debilitating	High need
Cold agglutinin disease	4,800	Severely debilitating	High need
Autoimmune orchitis	3,100	Moderately debilitating	High need
Anti-MAG Peripheral Neuropathy	2000	Moderately debilitating	High need
Cicatricial pemphigoid	1,700	Moderately debilitating	High need
Autoimmune retinopathy	1,550	Severely debilitating	High need
Lambert-Eaton Myasthenic Syndrome	1,300	Severely debilitating	High need
Goodpasture's syndrome	1,120	Debilitating	High need
Linear IgA disease (LAD)	950	Moderately debilitating	High need

Source: Stifel Research

Impressive Results of Argenx Efgartigimod in Myasthenia Gravis

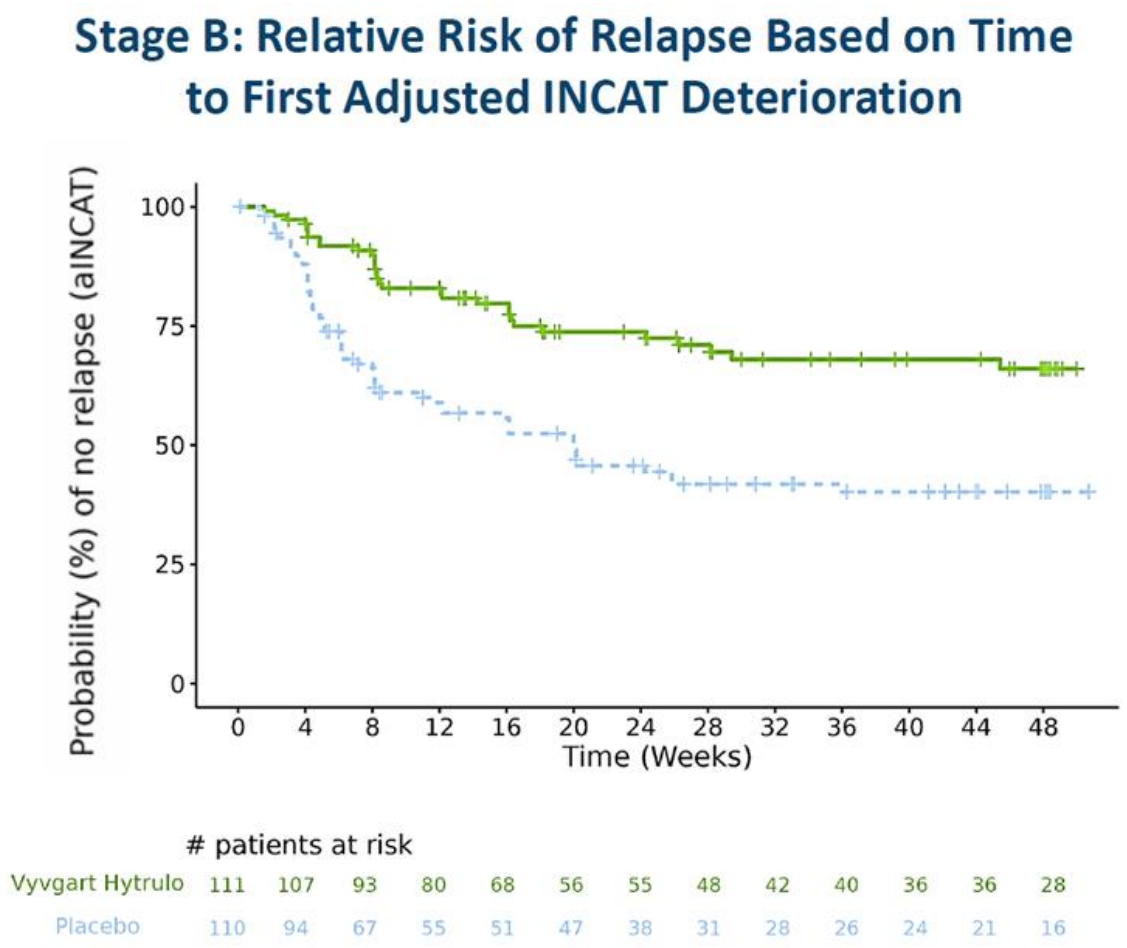
Howard JF Jr, Efgartigimod MG Study Group. Randomized phase 2 study of FcRn antagonist efgartigimod in generalized myasthenia gravis. *Neurology*. 2019 Jun 4;92(23):e2661-e2673.

Of the 35 screened patients, 24 were enrolled and randomized: 12 received efgartigimod and 12 placebo. Efgartigimod was well-tolerated in all patients, with no serious or severe adverse events reported, no relevant changes in vital signs or ECG findings observed, and no difference in adverse events between efgartigimod and placebo treatment. All patients treated with efgartigimod showed a rapid decrease in total immunoglobulin G (IgG) and anti-AChR autoantibody levels, and assessment using all 4 efficacy scales consistently demonstrated that 75% showed a rapid and long-lasting disease improvement.



Source: https://pubmed.ncbi.nlm.nih.gov/31118245/

Impressive Results of Argenx Efgartigimod in CIDP



Primary endpoint met

demonstrating a **61% lower risk of relapse** based on time to first adjusted INCAT deterioration with VYVGART Hytrulo compared to placebo

HR: 0.39
p = 0.000039

Clinical benefit observed across all efficacy scales and patient subgroups, regardless of prior therapy

Source: argenx corporate presentation, Sep 2023

Excellent Commercial Launch of Efgartigimod (VYVGART®)

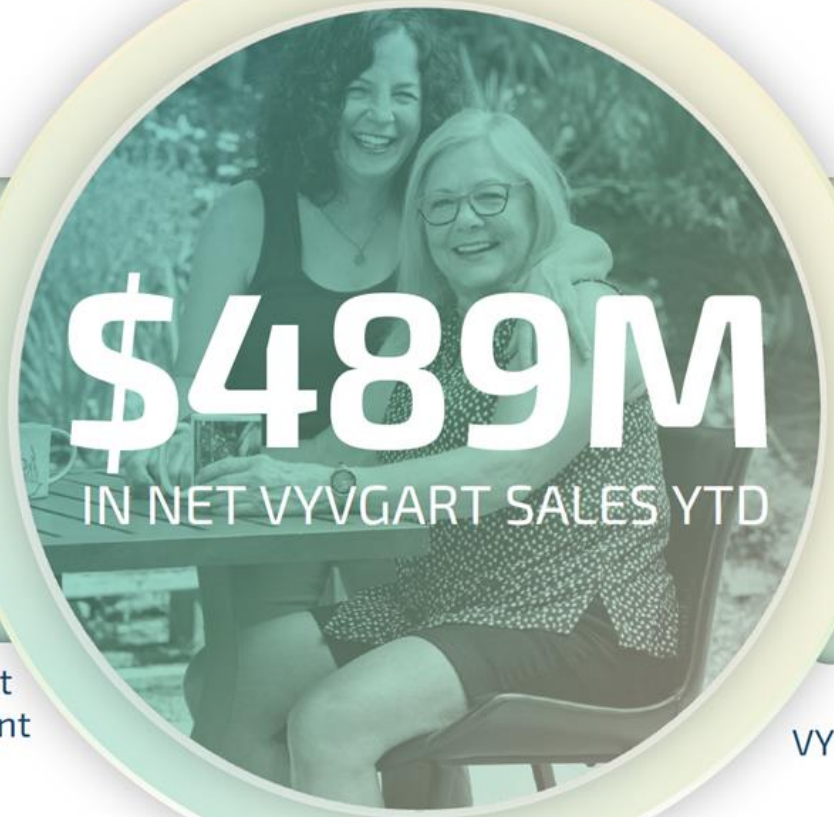
Optimizing Core Launch Strategies

VYVGART launched in US, Japan, Germany, Italy

SUBMISSIONS OR APPROVALS I
10+ COUNTRIES

Consistent prescriber growth to increase breadth of patients

>2,100 PRESCRIBERS
UNITED STATES



17,000 addressable gMG patients

Consistent growth looking at month over month new patient starts

Potential to drive earlier line uptake

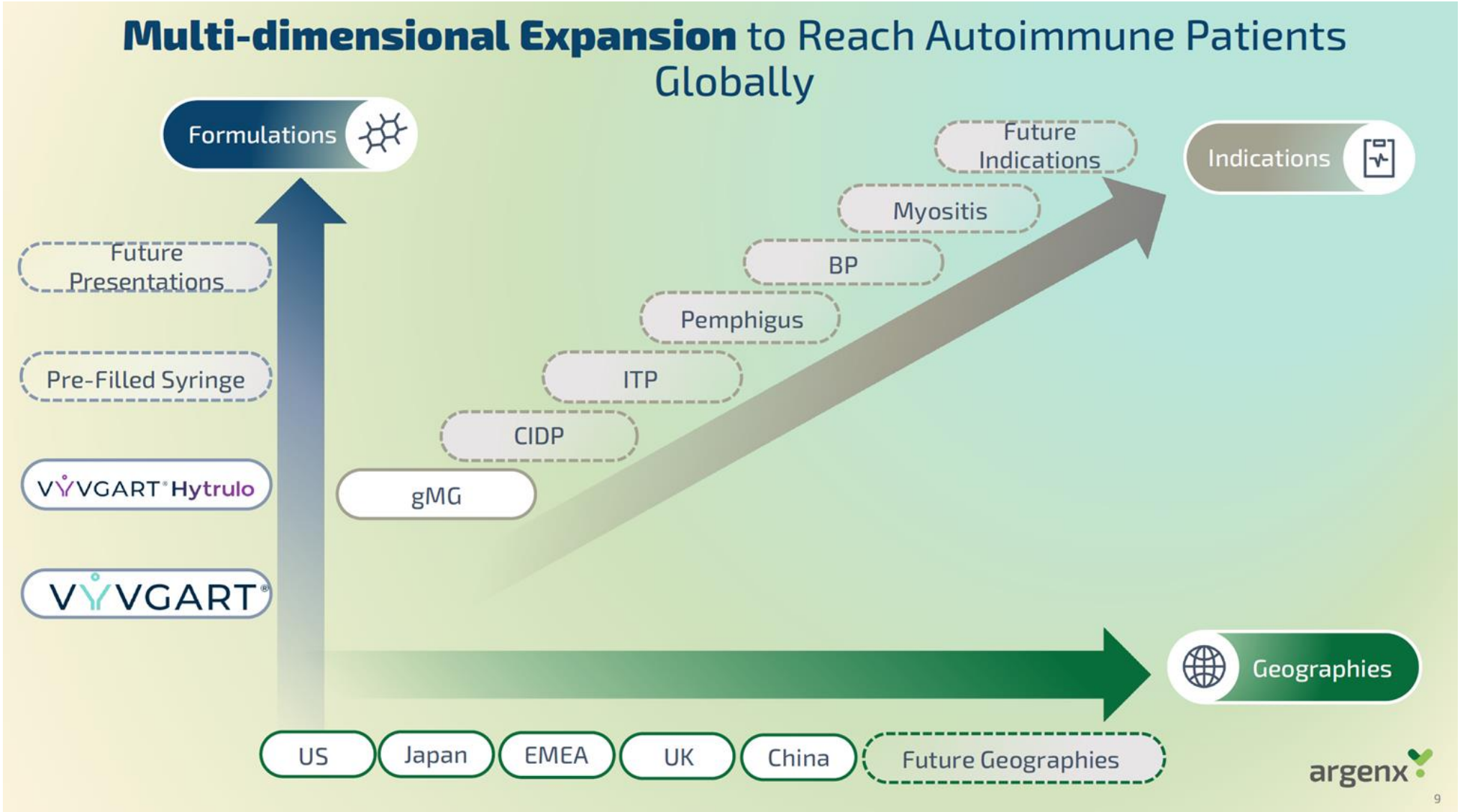
VYVGART Hytrulo launched in US

argenx

7

Source: argenx corporate presentation, Sep 2023

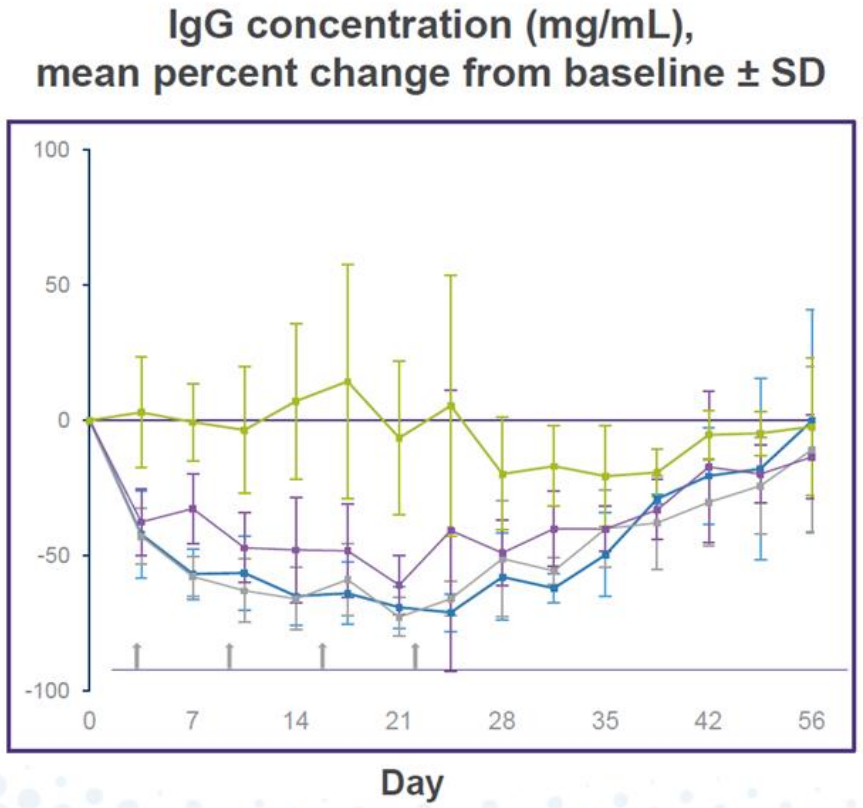
Argenx Expanding Indications and Formulations for VYVGART®



Source: Argenx corporate presentation, Sep 2023

Immunovant's IMVT-1402 Achieves Deep IgG Reductions

IMVT-1402 demonstrated similarly rapid and deep IgG reduction as batoclimab in a head-to-head monkey study



- 20 monkeys, dosed IV in head-to-head study across four groups
- At comparable doses, IgG lowering is similar for both batoclimab and IMVT-1402
- Cynomolgus monkeys observed to be reliable pharmacodynamic proxy for anti-FcRn mediated impacts on IgG[1,2]

Source: Immunovant Corporate Presentation, Sep 2023

Last Week Saw Immunovant Announce IMVT-1402 Results Without Reducing Albumin or LDL-C

NEW YORK, Sept. 26, 2023 (GLOBE NEWSWIRE) -- Immunovant, Inc. (Nasdaq: IMVT), a clinical-stage immunology company dedicated to enabling normal lives for people with autoimmune diseases, today announced that subcutaneously administered doses of IMVT-1402 produced dose-dependent reductions in IgG in initial data from a Phase 1 clinical trial in healthy adults, with no dose-related changes in serum albumin or LDL-C, bolstering IMVT-1402 as a potential best-in-class neonatal fragment crystallizable receptor (FcRn) inhibitor.

"We are encouraged by the strong pharmacodynamic data observed to date with IMVT-1402," said Pete Salzmann, M.D., chief executive officer of Immunovant. "These first-in-human results are consistent with those observed in prior non-human primate studies, and we look forward to sharing additional MAD data in November."

This Phase 1 clinical trial is a randomized, double-blind, placebo-controlled ascending dose study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of IMVT-1402 in healthy adults.

In the single-ascending dose (SAD) portion of the study, subcutaneously administered IMVT-1402 demonstrated a consistent reduction in IgG with potency that was similar to or greater than that of batoclimab. The safety data were generally favorable, with all adverse events (AEs) mild or moderate, and no significant reduction from baseline in serum albumin or increase in LDL-C observed at any timepoint measured (all $p>0.05$).

Immunovant is also pleased to announce that initial MAD study results for the 300 mg cohort were released ahead of schedule today. These data represent all the MAD data currently available. Dosing for the 600 mg cohort has recently begun. After four weekly 300 mg SC doses of IMVT-1402, the mean total IgG reduction from baseline in this MAD cohort was 63%, with no decrease in serum albumin below baseline and no increase in LDL-C above baseline observed. Treatment-emergent adverse events were observed to be mild or moderate in severity. IMVT-1402 was delivered subcutaneously in seconds to participants in this cohort as a simple 2 mL injection at a concentration of 150 mg/mL.

This is a big deal because the FcRn market is potentially so large. The ability of Immunovant to deliver an FcRn inhibitor that lacks an albumin binding liability opens up the potential to compete head on with argenx and J&J.

Source: https://www.immunovant.com/investors/news-events/press-releases/detail/51/immunovant-announces-positive-initial-imvt-1402-phase-1-sad

Biohaven Shares Rise Last Week After News on BHV-1300 IgG Degrader

Marketwatch, Sep 27, 2023

Biohaven shares rose sharply Wednesday after the biopharmaceutical company posted pharmacodynamic updates for its BHV-1300 bispecific immunoglobulin G, or IgG, degrader that showed greater than 90% reductions in IgG after repeat dosing.

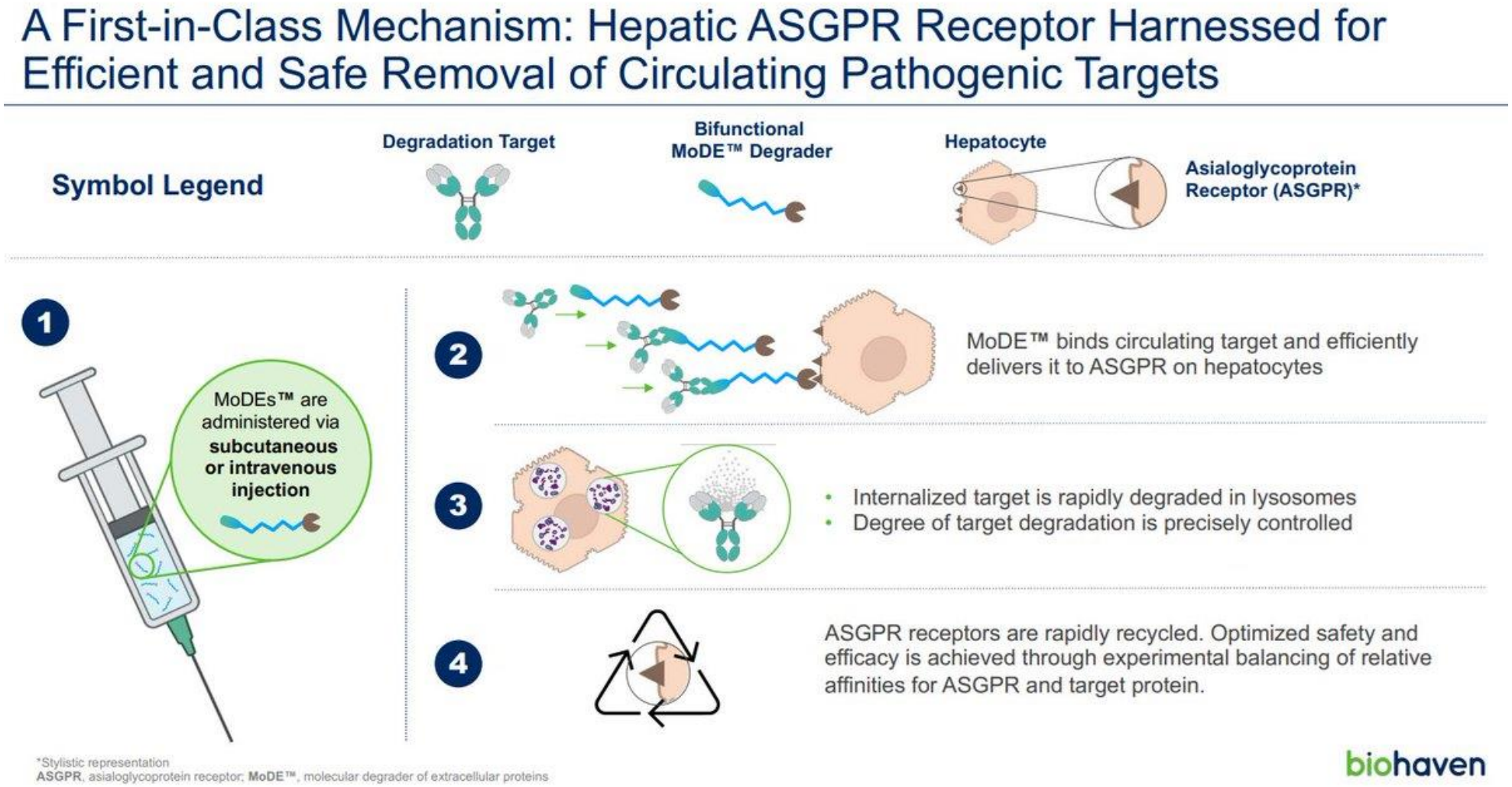
Shares of the New Haven, Conn., company were recently changing hands at $22.39, up 27%.

Biohaven disclosed the BHV-1300 information in an updated corporate presentation included in a filing with the U.S. Securities and Exchange Commission.

In the presentation, Biohaven said BHV-1300 showed faster depletion of IgG in a non-human primate compared with standard-of-care efgartigimod.

Source: https://www.marketwatch.com/story/biohaven-shares-rise-after-update-on-bhv-1300-igg-degrader-b0705288

Biohaven Introduces 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.

BHV-1300 Has High Capacity to Remove IgG

Hepatic ASGPR Receptor Harnessed for Efficient and Safe Removal of Pathogenic Targets

- High capacity ASGPR hepatocellular receptors internalize plasma proteins with specific motifs
- Bispecific ASGPR-binders with target-binder effectively removes pathogenic target from the circulation
- IgG may be more rapidly removed from the circulation than FcRN inhibitory antibody or antibody fragments, without causing hypoalbuminemia or dyslipidemia
  - Improved, dialable potency (deeper IgG/IgA reductions possible)
  - Improved pharmacodynamics (faster onset of action)
  - Improved safety profile (fewer side-effects, rapid drug elimination)

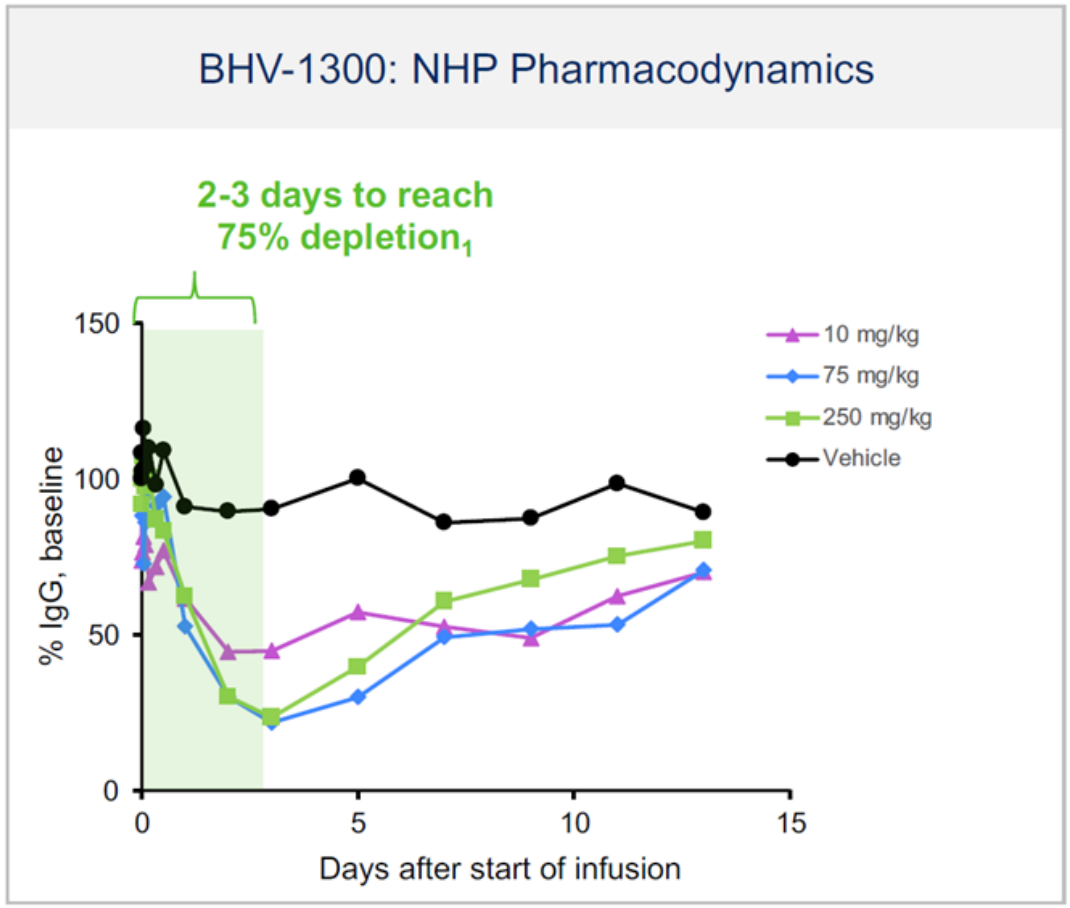
BHV-1300: A highly optimized Biohaven ASGPR binder advancing as drug candidate

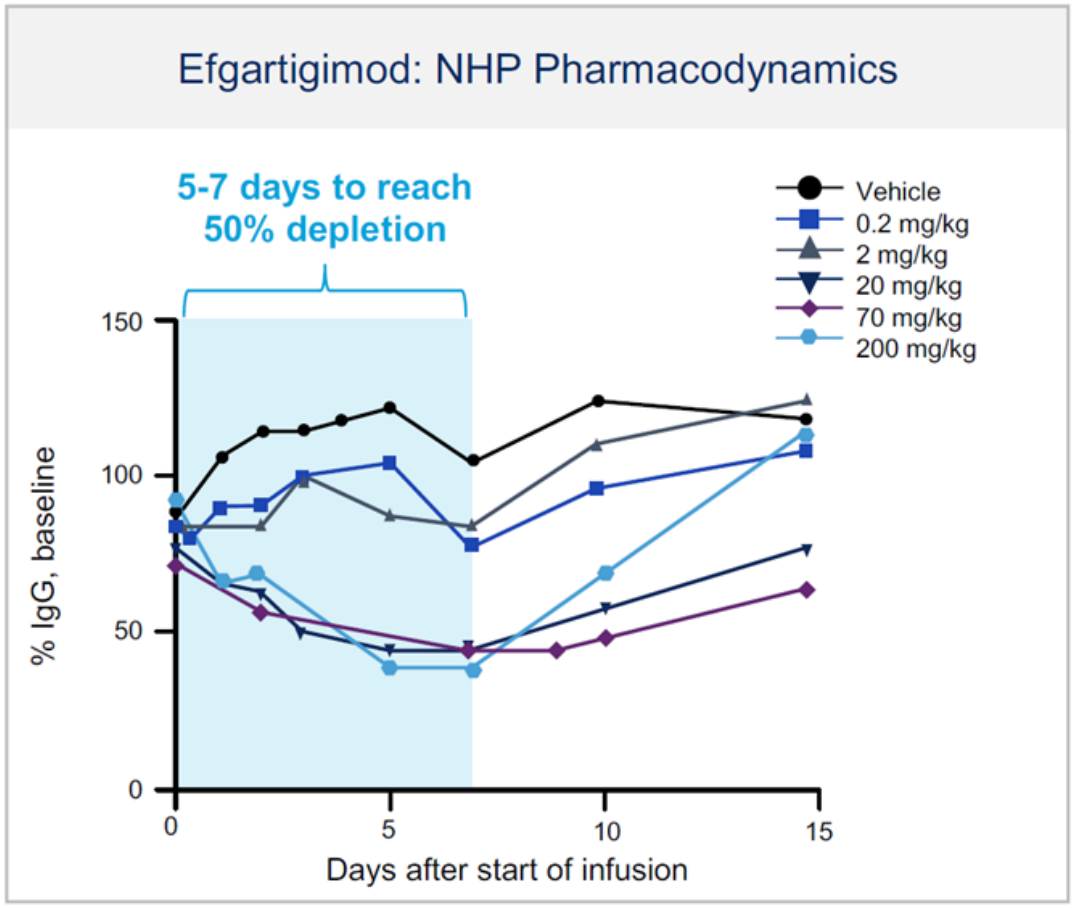
- ✓ Balances liver removal of unbound to target-bound drug
- ✓ Optimizes safety vs efficacy
- ✓ Improves kinetics of target removal
- ✓ Suitable Target Product Profile for a rapid onset medication with weekly or less frequent SC administration

Sources: Biohaven Corporate Presentation, Sep 2023.

BHV-1300: Shows Potential for Superiority Over SOC (Efgartigimod)

BHV-1300 demonstrated faster depletion of IgG in a non-human primate (NHP) compared to efgartigimod





1. deeper reductions (~90%+) possible with multiple dosing

The Journal of Clinical Investigation 2018:128(10):4372-4386. https://doi.org/10.1172/JC197911.
IgG, immunoglobulin G; **NHP**, non-human primate; **SOC**, standard of care

biohaven

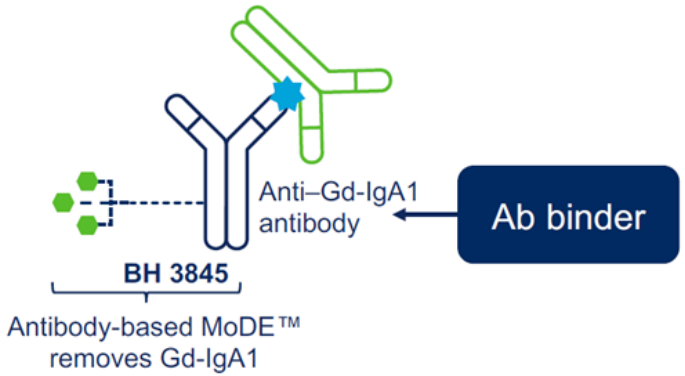
Source: Biohaven Corporate Presentation, Sep 2023

Separately, Biohaven Can Target Specific Ig's with its Degraders

Preclinical Studies Show the Gd-IgA1–Specific MoDE™ Selectively Degrades the Gd-IgA1 Present in IgAN

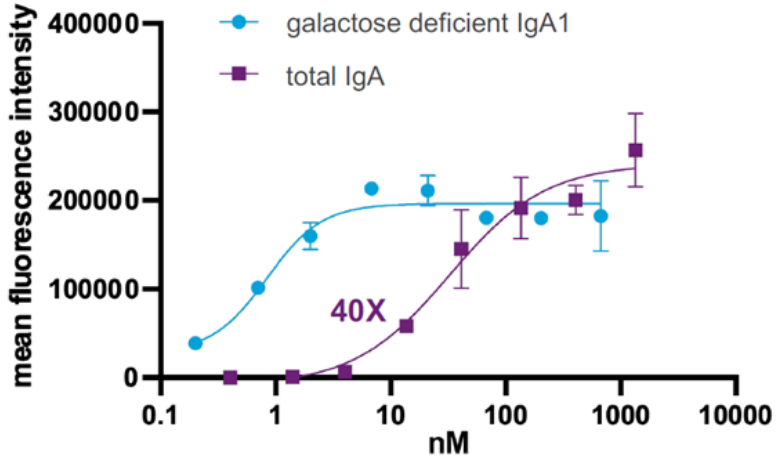
At low concentrations, this Gd-IgA1–specific MoDE™ selectively degrades Gd-IgA1 and spares total IgA, limiting the impact on the immune system

Gd-IgA1–Specific MoDE™



- Reduces only pathogenic Gd-IgA1
- Spares IgA, limiting immune impacts

Gd-IgA1–Specific MoDE™ Selectively Degrades Gd-IgA1



	EC_{50}
Galactose deficient IgA1	0.84
Total IgA	33

biohaven

Ab, antibody; **EC_{50}**, half maximal effective concentration **Gd**, galactose-deficient; **Ig**, immunoglobulin; **IgAN**, IgA nephropathy; **MoDE™**, molecular degrader of extracellular proteins

BHV-1300: Has Potential to Add Significant Value Across Rare And Common Diseases With a Differentiated Profile from FcRn Class

BHV-1300 DIFFERENTIATED FROM COMPETITORS
in FcRn class such as efgartigimod and nipocalimab with a **unique MOA, faster onset, and predicted to have improved safety**

PHASE 2 STUDY
Start in 2024

biohaven

biohaven

Source: Biohaven Corporate Presentation, Sep 2023

ASGPR-Targeting Chimeras (ATACs): A New Class of Degraders

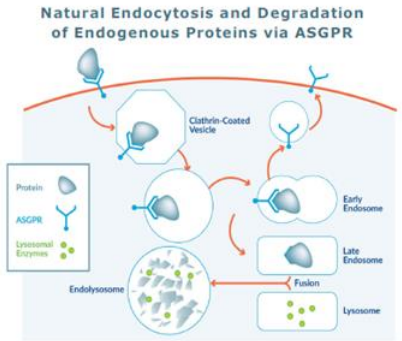
Srinivasa R. Karra, Alison J. Davis, Jessica E. Friedman, Ron de Jong, Jesse J. Chen, Kevin J. Lumb, Jason A. Wiles
Avilar Therapeutics, Waltham, MA, USA

Abstract

Targeted protein degradation is a promising new therapeutic modality that enables the removal of disease-causing proteins. First-generation protein degradation technologies have utilized the ubiquitin proteasome system to successfully degrade intracellular proteins. Recently, a new and attractive approach has emerged that enables the endolysosomal degradation of extracellular proteins using the asialoglycoprotein receptor (ASGPR), an endocytotic receptor expressed predominantly on the surface of hepatocytes. Various endogenous circulating extracellular glycoproteins are internalized via clathrin-mediated endocytosis and then degraded in the hepatocyte endolysosome. We describe herein the development of a novel ASGPR-targeting chimera (ATAC) platform using bifunctional compounds containing Avilar's novel, potent, small-molecule ASGPR-binding ligands. For initial proof-of-concept studies, ATACs were designed designed with Avilar's proprietary technology to target two extracellular proteins with different concentration and kinetic properties: one with high plasma concentration and a long half-life, the other with low plasma concentration and short half-life. In vitro characterization of the ATAC interactions with ASGPR and the target proteins, including binding, cellular uptake, and degradation via the endolysosomal pathway will be presented.

ASGPR Key Role in Body's Natural Cellular Degradation Machinery

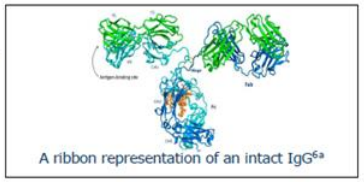
- ASGPR offers natural cellular machinery for extracellular degradation, analogous to E3 ligases in intracellular degradation
- Cell surface receptor mediates the endocytosis and degradation of various endogenous glycoproteins in endolysosome
- Highly expressed on hepatocytes (~1M receptors per cell in humans)
- Endocytosed and recycled from endosome back to plasma membrane every ~15 minutes

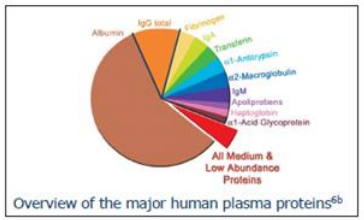


Proprietary Technology Platform to Design and Build ATACs

ATAC Platform PoC Using Immunoglobulin G (IgG), a High Plasma Concentration and Long Half-Life Protein

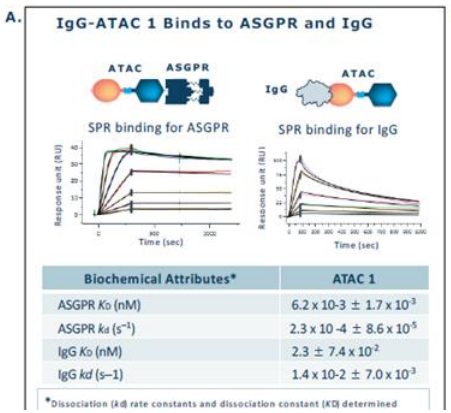
- To exemplify our ATAC platform, we designed ATAC molecules to target and degrade IgG, a high plasma concentration and long half-life extracellular protein
- IgG is a ~146 kDa antibody and it is the major class of immunoglobulins
- IgG binds to cell surface receptors on many types of cells to trigger phagocytosis or antibody-dependent cellular cytotoxicity[5a]
- IgG is the second most abundantly available and most common type of antibody found in blood
- IgG concentration[5b]
  - 1.06 g/kg total body IgG = 74.2 g total in 70 kg human = 508 µmol
- Resynthesis properties
  - $t_{1/2}$: 21 days
  - 32 mg/kg/day = 2.2 g/subject/day = 15 µmol/day
  - ~3% of total body IgG


A ribbon representation of an intact IgG[6a]



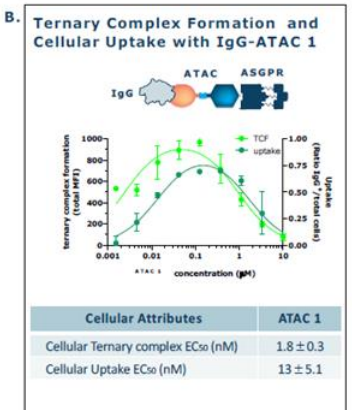
Overview of the major human plasma proteins[6b]

ATAC **1** Binds to IgG and ASGPR and Depends on ASGPR for Activity



Biochemical Attributes*	ATAC 1
ASGPR K_D (nM)	6.2 x 10-3 ± 1.7 x 10^{-3}
ASGPR k_d (s^{-1})	2.3 x 10 -4 ± 8.6 x 10^{-5}
IgG K_D (nM)	2.3 ± 7.4 x 10^{-2}
IgG k_d (s^{-1})	1.4 x 10-2 ± 7.0 x 10^{-3}

*Dissociation (k_d) rate constants and dissociation constant (K_D) determined



Cellular Attributes	ATAC 1
Cellular Ternary complex EC_{50} (nM)	1.8 ± 0.3
Cellular Uptake EC_{50} (nM)	13 ± 5.1

Like Biohaven, Avilar Theraputics, a private biotech backed by RA Capital and Sanofi, has been able to achieve binding and disposal of IgG using ASPGR targeted degraders.

Source: https://avilar-tx.com/wp-content/uploads/2022/05/ASGPR-Targeting-Chimeras-ATACs.pdf

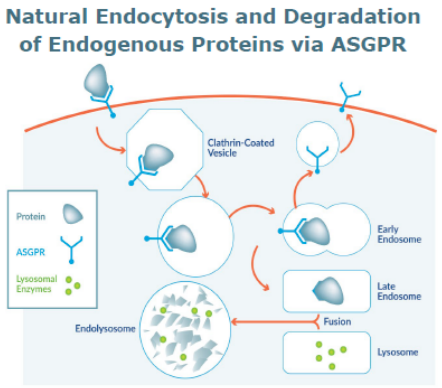
Avilar Therapeutics Showed Significant IgG Degradation in Monkeys With Repeat Dosing in 2022

Abstract

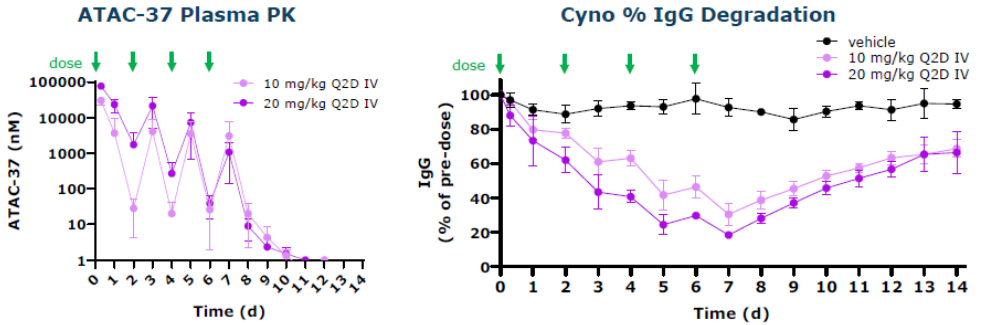
A new targeted protein degradation approach has emerged that enables the endolysosomal degradation of extracellular proteins via the asialoglycoprotein receptor (ASGPR), an endocytic receptor expressed predominantly on the surface of hepatocytes. Here we describe the development of a new ASGPR targeting chimera (ATAC) platform using bifunctional molecules containing Avilar's novel, potent, small-molecule ASGPR-binding ligands. For proof-of-concept studies, ATACs were designed to target the extracellular protein IgG, a high plasma concentration and long half-life protein. In vitro characterization of the ATAC interactions with ASGPR and IgG revealed potent biochemical binding, ASGPR-mediated cellular uptake, and degradation of IgG via the endolysosomal pathway. A heterologous rat PK/PD model was used to test ATAC-mediated depletion of human IgG. Human IgG injected IV in rats was depleted from plasma within 4 hours after ATAC dose. Rat liver PK and histology revealed ATAC-dependent uptake of IgG into hepatocytes, subsequent trafficking of IgG to the endolysosome and degradation of IgG in vivo. ATAC-dependent depletion of endogenous IgG was also achieved in cynomolgus monkey, reaching 35% after a single dose and 85% after repeat dosing.

ASGPR Role in Body's Natural Cellular Degradation Machinery

- Cell surface receptor and part of natural cellular machinery for extracellular degradation[1,2] (like E3 ligases in intracellular degradation)
- Mediates the endocytosis and degradation of various endogenous glycoproteins in endolysosome[1,2]
- Highly expressed on hepatocytes (~1M receptors per cell in humans)[1,2]
- Endocytosed and recycled from endosome back to plasma membrane every ~15 minutes[1,2]



Repeat Dose IV of Bidentate ATAC-37 Degrades > 80% IgG in NHP



- Q2D dosing to accommodate short 5 day cyno IgG half-life
- Dose-dependent ATAC-37 exposure and IgG degradation after repeat dose
- 20 mg/kg: 27% (10 μM) at 24 h and max 82% (32 μM) at 7 d

Figure legend. PK and PD profiles of ATAC-37 in cyno PK/PD model. Vehicle or ATAC-37 was dosed at 10 or 20 mg/kg IV every 2 days for 4 cycles in cynomolgus monkeys. Blood samples were taken at various time points and plasma was processed for PK and PD measurements. **Left.** ATAC-37 concentration (nM) by LC/MS/MS. **Right.** Cyno IgG levels by ELISA expressed as a percent of the predose time point. Green arrows depict dosing days.

Repeat Dosing of ATAC-37 Does Not Affect Albumin, LDL levels

ATAC-37 does not decrease albumin levels while decreasing IgG levels by 70%

ATAC-37 does not increase LDL levels

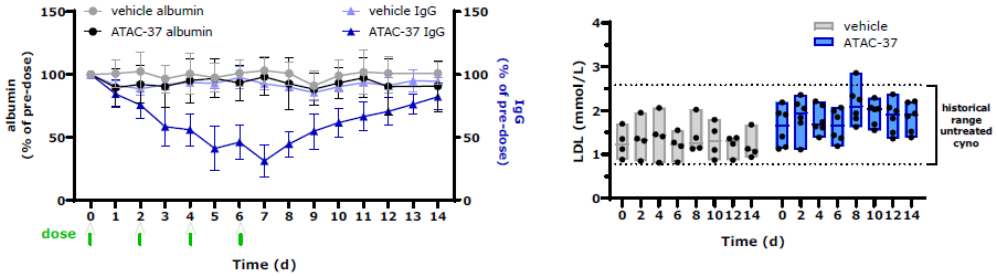


Figure Legend. ATAC-37 was dosed IV at 20 mg/kg 4 times Q2D in cynos. **Left panel:** IgG and albumin levels measured by ELISA. Graph represents the mean +/-SD of n=4 vehicle or n=6 treated cynos per group. **Right panel:** LDL measured in cyno plasma using clinical chemistry panel. Boxplot shows min to max values with lines at the median and all individual data points for n=4 vehicle and n=6 ATAC-37 treated cynos. Dotted lines show historical normal range of LDL levels in untreated cyno.

Source: https://avilar-tx.com/our-science/posters-publications/

Illustration of ASPGR Degrader Approach Versus PROTAC

PROTAC

Biohaven LYTAC

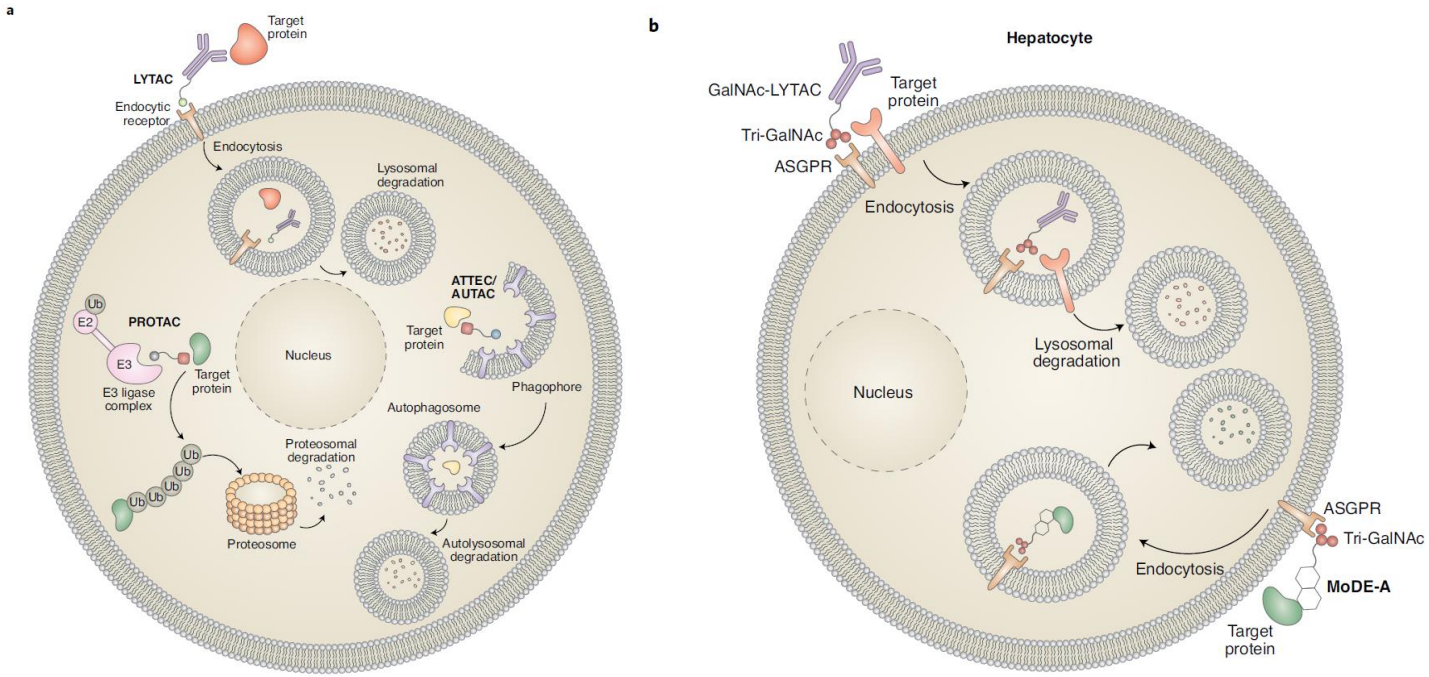


Fig. 1 | Comparison of TPD mechanisms: from PROTA Cs to GalNAc-LYTA Cs. a, PROTACs degrade protein targets by bridging interactions between an E3 ligase complex and a given target, promoting ubiquitination (Ub) and proteosomal degradation; AUTACs and AUTTECs recruit targets to phagophores to induce degradation through the autophagy pathway; LYTACs bind and degrade extracellular targets by hijacking endocytic receptors that are subsequently endocytosed and trafficked to the lysosome. b, Mediated by a tri-GalNAc functionality, GalNAc-LYTACs and synthetic bifunctional MoDE-As bind ASGPR expressed on hepatocytes to coordinate tissue-selective target degradation via the lysosomal pathway.

Source: https://www.nature.com/articles/s41589-021-00835-1

Considerations with ASPGR LYTAC Approach

While the Biohaven BHV-1300 and Avilar IgG disposal approach is highly promising there are a number of considerations that this drug class will need to address over time:

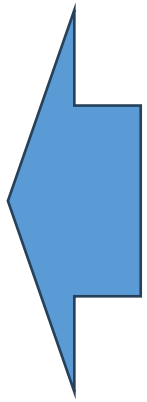
Performance in humans relative to performance in monkeys.
Ability to access and recycle IgG may be challenging in extracellular space.
Kinetics of drug in humans and dosing interval.
Management of potential risk of wiping out all accessible IgG.
Potential dependency of versions of technology on IgG glycosylation subtypes.[1]
Degree of degradation and speed of GalNAc-LYTAC recycling possible through ASPGR sites in liver.[2]

1. See https://patents.google.com/patent/WO2022192478A1
2. See https://www.nature.com/articles/s41589-021-00770-1 and https://www.nature.com/articles/s41589-021-00835-1

Comparison of ASPGR Degradation to FcRn Inhibitors: Pharmacokinetics (PK)

Ahn G, Banik SM, Miller CL, Riley NM, Cochran JR, Bertozzi CR. LYTACs that engage the asialoglycoprotein receptor for targeted protein degradation. Nat Chem Biol. 2021 Sep;17(9):937-946.

We observed that site-specifically labeled Ctx conjugates maintained similar binding to EGFR but exhibited lower uptake efficiency in HEPG2 cells than the non-specific conjugates (Extended Data Fig. 8a,b). Based on these results, we asked whether site-specifically labeled conjugates might exhibit altered in vivo clearance profiles. To test this, BALB/c mice were intraperitoneally injected with 5 mg kg^{-1} of Ctx, non-specifically conjugated Ctx-$(GalNAc)_{10}$, Ctx-C-term-$(GalNAc)_1$ or Ctx-CH1-$(GalNAc)_1$, and plasma was collected at 6, 24, 48 and 72 h to analyze their clearance rate. Ctx-$(GalNAc)_{10}$ cleared rapidly before 6 h (Fig. 6d), implying frequent treatments would be required to maintain reduced EGFR levels given that degradation was not durable for more than 24 h in vitro following wash-off after LYTAC treatment (Extended Data Fig. 9). However, site-specific conjugates showed an initial clearance followed by sustained presence 72 h after injection (Fig. 6d,e), demonstrating that site-specific GalNAc-LYTACs may be advantageous in vivo due to less frequent dosing versus non-specific conjugates, thereby enhancing the potential for sustained degradation of membrane targets. However, non-specific conjugates may be preferred for rapid clearance of soluble targets.



Thus far, Biohaven has not published data on the PK of BHV-1300 but instead has focused in on the pharmacodynamics in a cynomolgus monkey. This publication on the technology notes that getting 72-hour presence of the LYTAC conjugate is possible but not trivial. That means that for BHV-1300 to match efgartigimod's 75% IgG knockdown, one would need to use BHV-1300 every week or so given that IgG has a life, on average, of around 30 days. Compare this to once every four weeks with efgartigimod.

Source: https://pubmed.ncbi.nlm.nih.gov/33767387/

Comparison of ASPGR Degradation to FcRn Inhibitors: Absolute Versus Relative Targeting

Illustrative "swarm drone attack"

Think of Biohaven's degraders as anti-aircraft guns shooting down a swarm of drones over Ukraine at night. If there are too many drones, then the effort might fail as the swarm overwhelms the defense. In contrast, if there are too few drones, the anti-aircraft fire will get all of them.

Human IgG volumes are variable and depend on many aspects of an organism including its weight, recent immune experience etc.* It is, in general, undesirable to knock out all IgG as they are important for infection control. But, if you don't get enough, the autoimmune disease persists.

Calibrating the volume of drug will be a critical issue for BHV-1300. We don't doubt that this can be worked out but wish to note that the problem is not trivial given the many variables involved.

In contrast, no matter how much of an FcRn inhibitor one can give to a patient there is a finite lower bound to the amount of IgG that can be removed. That's because an FcRn inhibitor reduces the half life of IgG without eliminating it at all.

In this sense, the argenx approach is much safer for patients because there will always be an IgG reservoir left to protect a patient against disease. The argenx approach is a relative one, reducing the proportion of IgG without absolute elimination.

* Source: https://pubmed.ncbi.nlm.nih.gov/35583717/

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

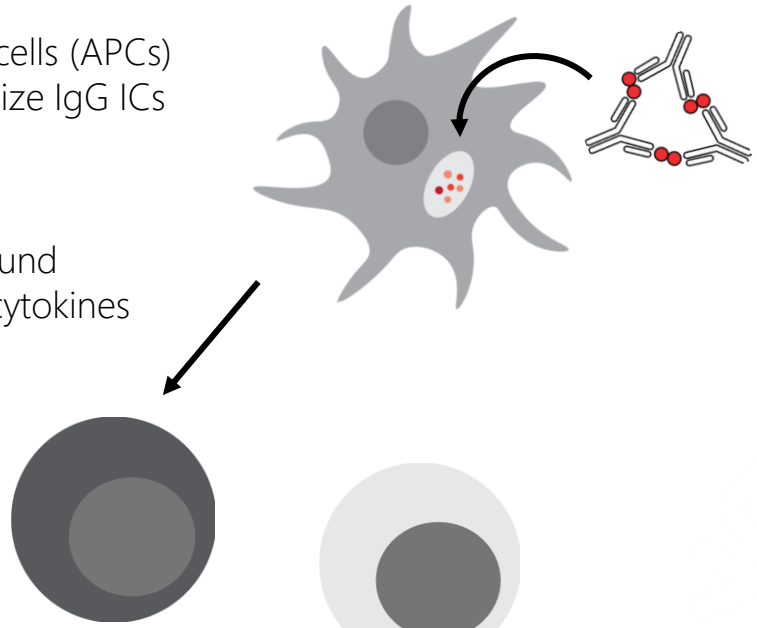
FcRn Directly Promotes Processes That Drive Potent and Wide-Reaching Immune Responses

IgG ICs modulate the immune in the following manner:

Antigen presenting cells (APCs) engage and internalize IgG ICs

APCs present IC-bound antigens & release cytokines

The above processes lead to:



Primed CD4+ T cells[1]

Primed CD8+ T cells[2,3]

Inflammation[4,5,7] and innate immunity[6]

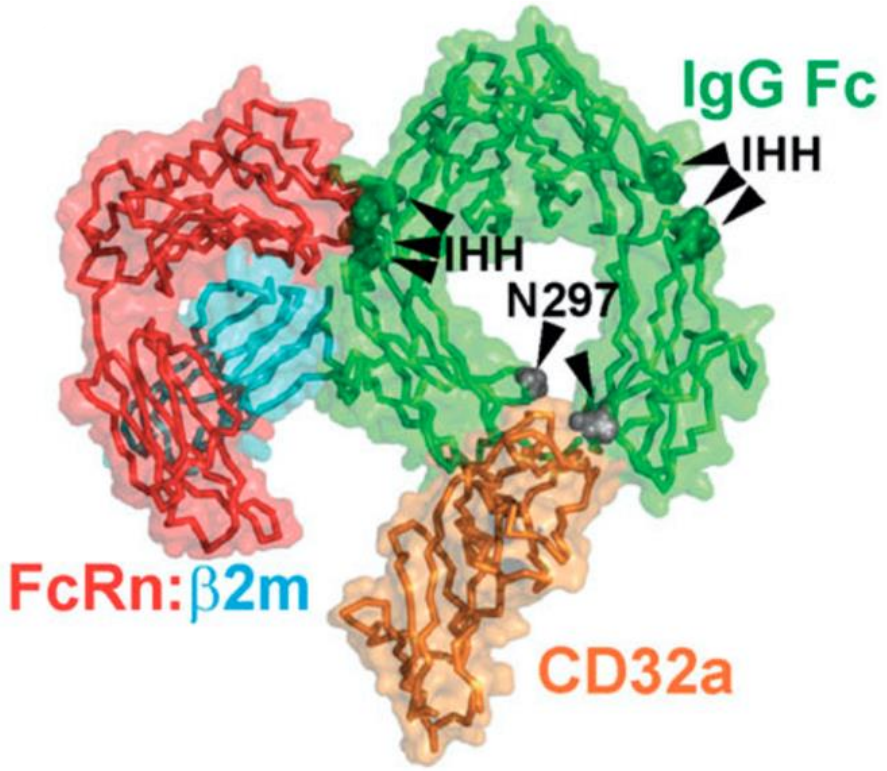
Key insights linking FcRn to these processes:

- FcRn is required for IgG IC induced CD4+ / CD8+ T cell priming[1,2,3] and the release of cytokines, such as TNFa and IL-6 by APCs
- Consistent with known disease associations, CD32A-131H promotes stronger IgG IC-mediated T cell priming[5] and inflammation[5]

When induced by auto-reactive IgG ICs, these processes can drive strong and persistent autoimmunity

1. Qiao et al., *PNAS*, 2008; Baker et al., *PNAS*, 2011; 3. Baker et al., *Immunity*, 2013; 4. Blumberg et al., *Science Advances*, 2019; 5. Hubbard et al., *J Exp Med*, 2020; 6. Castro et al., *Immunity*, 2019; 7. Pyzik et.al, Nature Reviews Immunology, 2023

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]

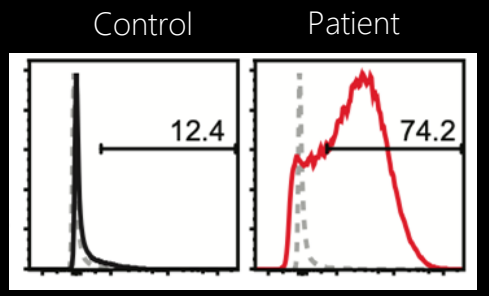
1. Hubbard et al., *J Exp Med*, 2020; 2. Cines et al., *Blood*, 2020

Immune Complexes of IgG, FcRn and Fcγ Responsible for Many Autoimmune Diseases

Today's focus on auto-antibodies and FcRn blockers masks the reality that a substantial fraction of autoimmunity involves the simultaneous interaction of IgG with Fc gamma receptors in a manner that is difficult to address with current approaches.

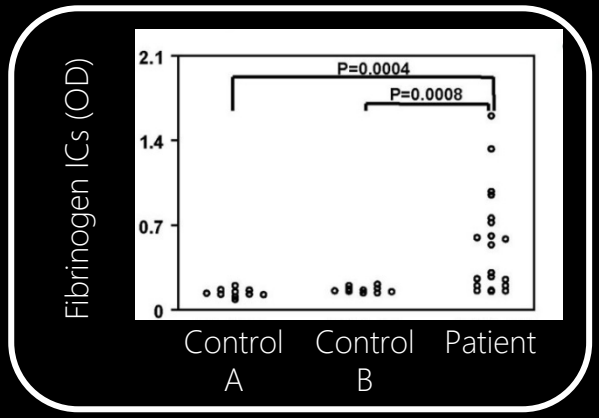
Immune complexes have been found in:

Ulcerative colitis (UC)[1]



Incidence:
38,000 new cases per year[2]

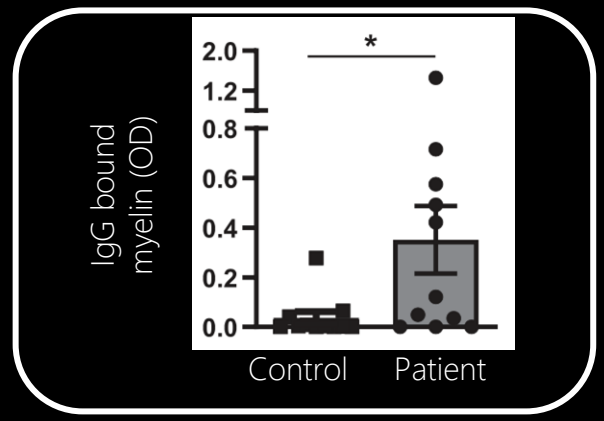
Rheumatoid Arthritis (RA)[3]



Incidence:
32,000 new cases per year[4]

50% patients present with auto-antibodies[4]

Multiple Sclerosis (MS)[5]



Incidence:
10,000 new cases per year[6]

1. Castro et al., *Immunity*, 2019; 2. Shivashankar et al., *Clin Gastroenterol Hepatol*, 2017; 3. Zhao et al., *Arthritis Res Ther*, 2008; 4. Myasoedova et al., *Ann Rheum Dis*, 2020; 5. Van der Poel et al., *J Immunol*, 2020; 6. http://www.msdiscovery.org/map-of-MS-prevalence;

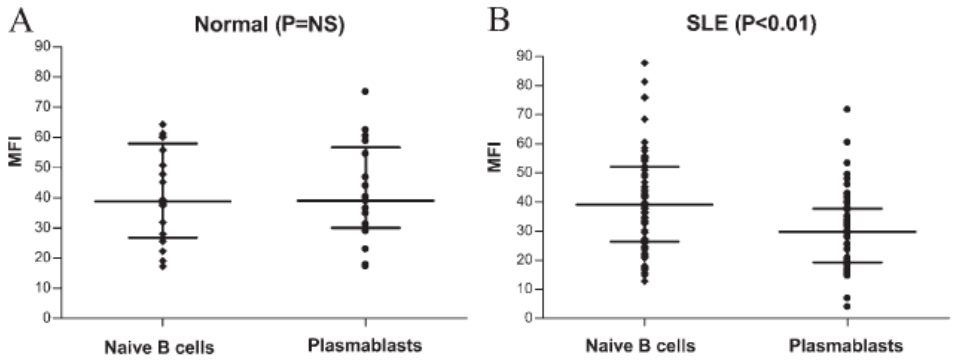
The Importance of FcγIIB in Autoimmunity

Selective dysregulation of the FcγIIB receptor on memory B cells in SLE

Meggan Mackay,[1] Anfisa Stanevsky,[1] Tao Wang,[1] Cynthia Aranow,[1] Margaret Li,[2] Scott Koenig,[3] Jeffrey V. Ravetch,[4] and Betty Diamond[1]

[1]Department of Medicine, Columbia University Medical Center, New York, NY 10032
[2]Department of Medicine, Albert Einstein College of Medicine, Bronx, NY 10461
[3]MacroGenics Inc., Rockville, MD 20850
[4]The Rockefeller University, New York, NY 10021

The inappropriate expansion and activation of autoreactive memory B cells and plasmablasts contributes to loss of self-tolerance in systemic lupus erythematosus (SLE). Defects in the inhibitory Fc receptor, FcγRIIB, have been shown to contribute to B cell activation and autoimmunity in several mouse models of SLE. In this paper, we demonstrate that expression of FcγRIIB is routinely up-regulated on memory B cells in the peripheral blood of healthy controls, whereas up-regulation of FcγRIIB is considerably decreased in memory B cells of SLE patients. This directly correlates with decreased FcγRIIB-mediated suppression of B cell receptor–induced calcium (Ca^{2+}) response in those B cells. We also found substantial overrepresentation of African-American patients among those who failed to up-regulate FcγRIIB. These results suggest that the inhibitory receptor, FcγRIIB, may be impaired at a critical checkpoint in SLE in the regulation of memory B cells; thus, FcγRIIB represents a novel target for therapeutic interventions in this disease.



Plasmablasts of SLE patients have reduced expression of FcγRIIB. Naive B cells were identified as $CD19_+$, $CD27_-$ and plasmablasts as $CD19_+$, $CD27_{++}$. Expression of FcγRIIB was determined by subtracting the MFI of the isotype control antibody from the MFI of the anti-FcγRIIB

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2118390/

Start-Ups Focusing on FcγIIB Agonism

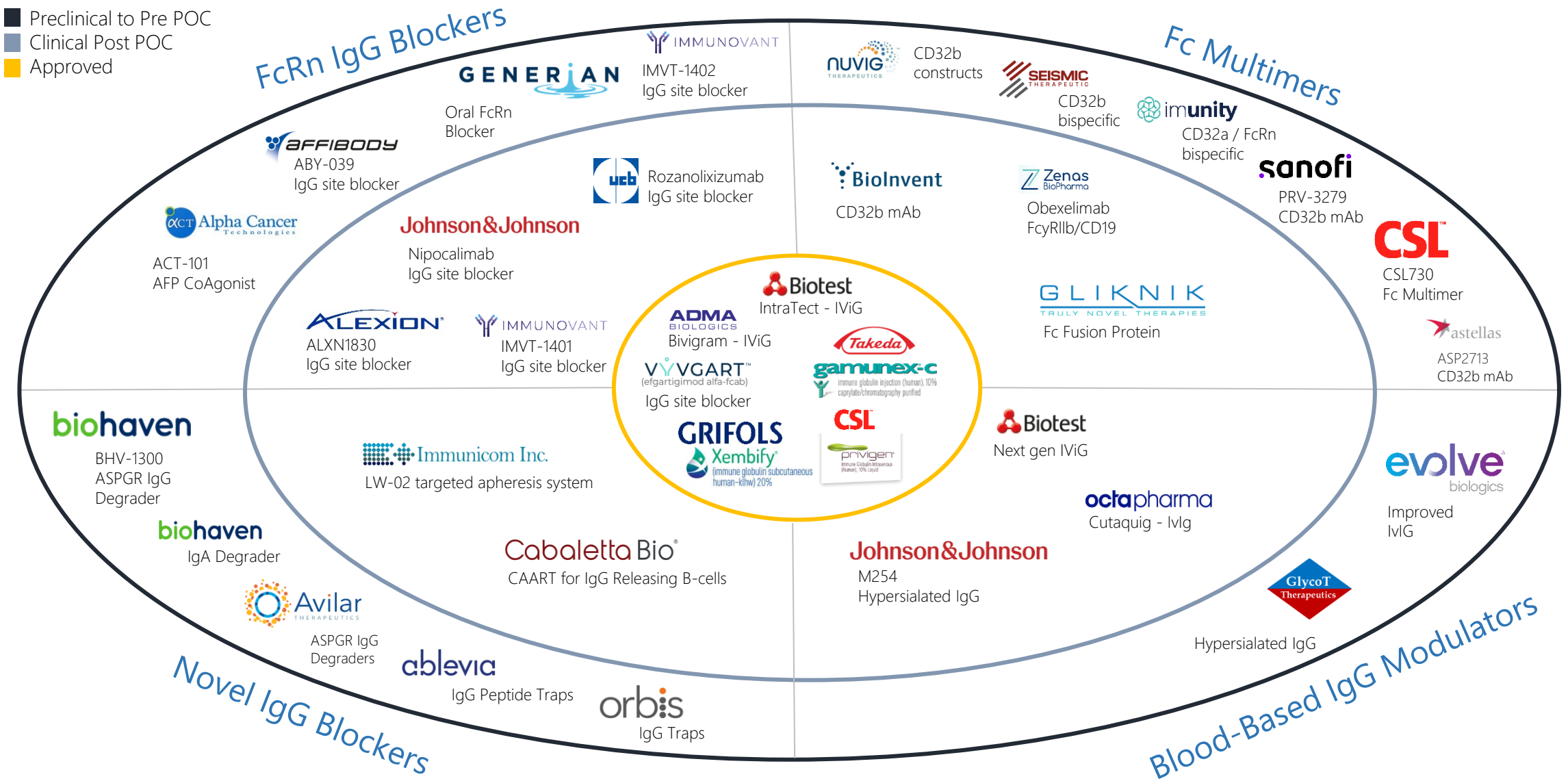
Website: https://www.nuvigtherapeutics.com/

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.

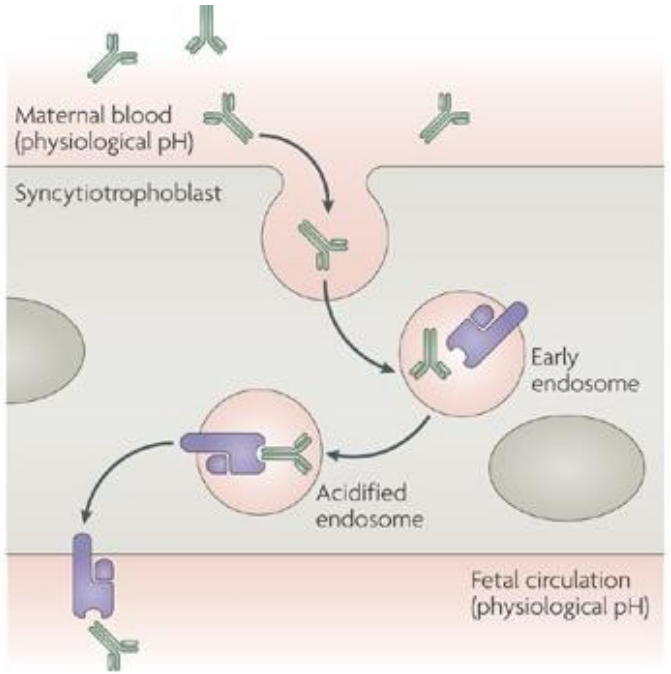
Pipeline of FcRn Antagonists, Fc Multimers and Novel IgG Blockers



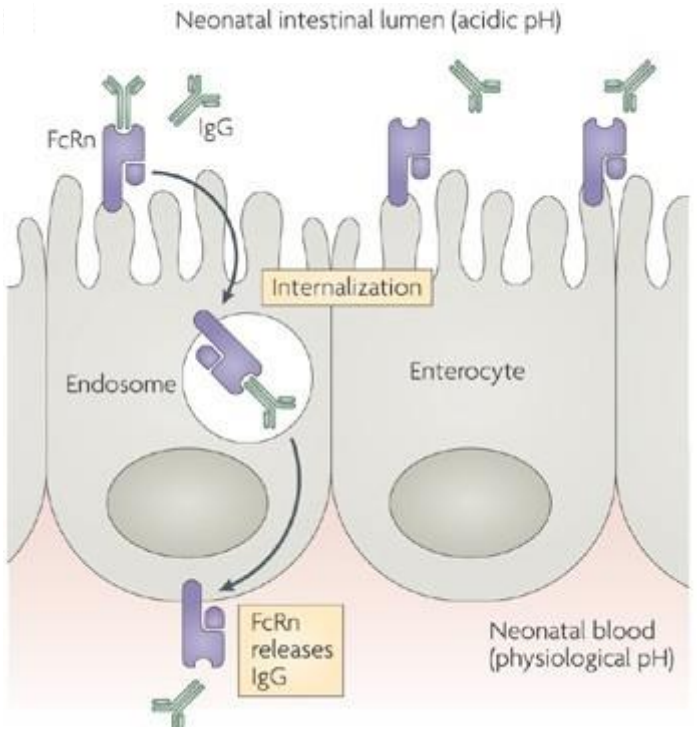
Source: Stifel Research

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

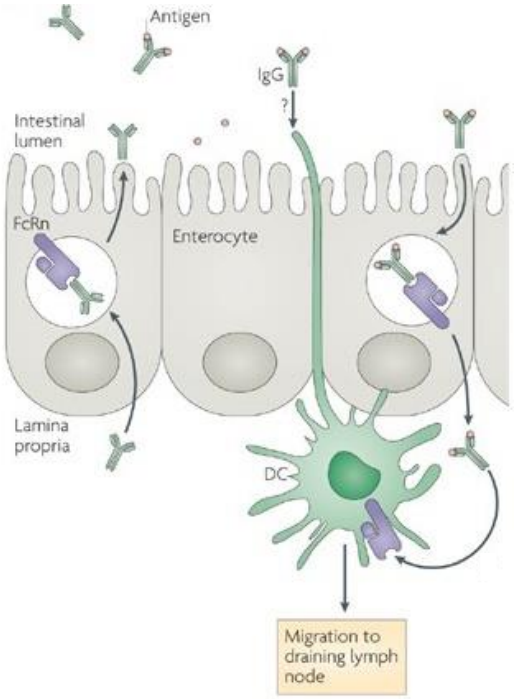
FcRn transports IgG from the maternal into the fetal circulation



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



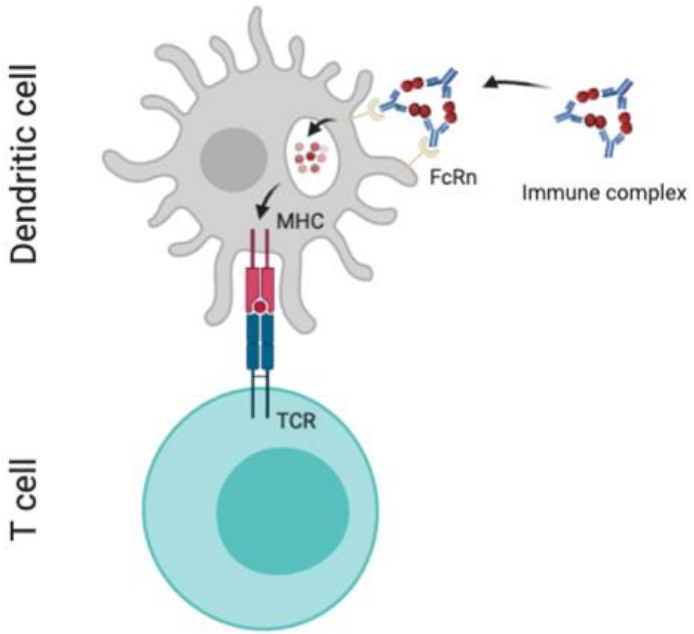
FcRn mediates trans-epithelial transfer of antigen bound IgGs, which then get taken up by DCs to prime adaptive immune responses



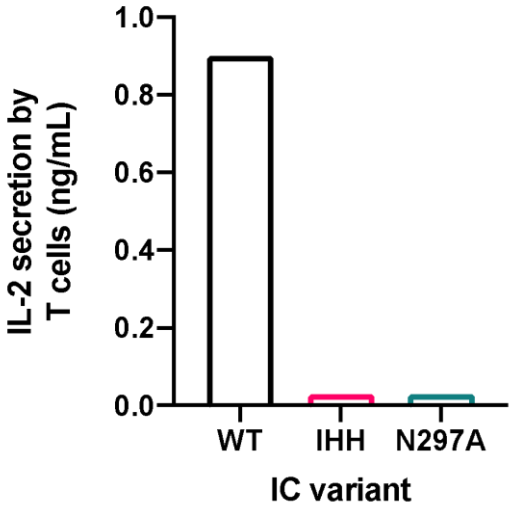
Roopenian et al., *Nature Reviews Immunology*, 2007

Priming of Adaptive Immunity is FcRn's Most Underappreciated Function

Dendritic cells (DCs) recycle IgG monomers, but process and present immune complexes (ICs) to T cells



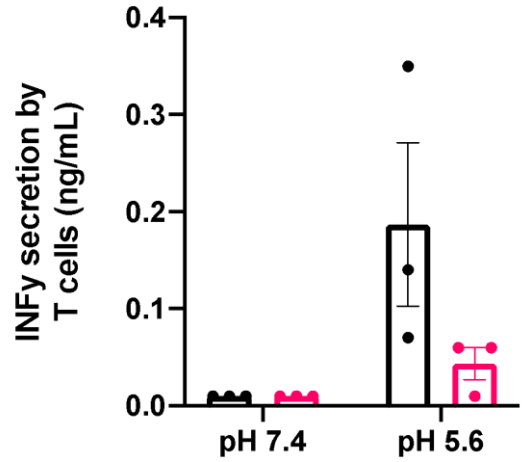
IC mediated T cell stimulation by DCs requires FcRn and FcγRs



IHH: Doesn't bind FcRn
N297A: Doesn't bind FcyRs

Baker et al., ***PNAS***, 2011

FcRn can mediate priming in the absence of FcγRs under acidic extracellular pH

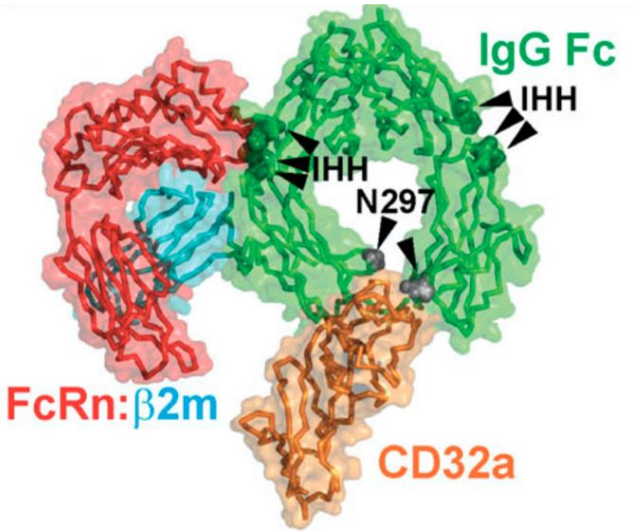


WT
IHH: Doesn't bind FcRn

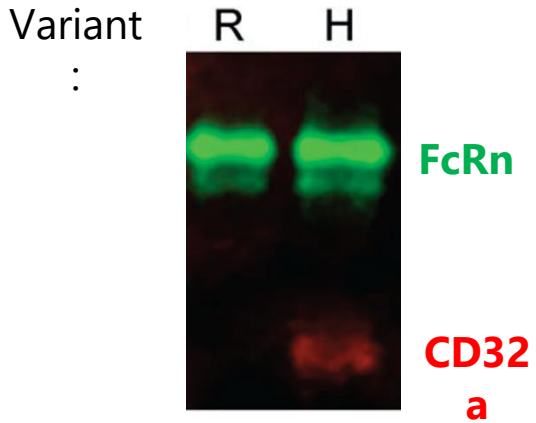
Hubbard et al., ***Journal of Clinical Investigation***, 2020

FcRn Cooperates With FcγRs in Priming and the Strength of this Association Impacts the Level of Downstream T Cell Activation

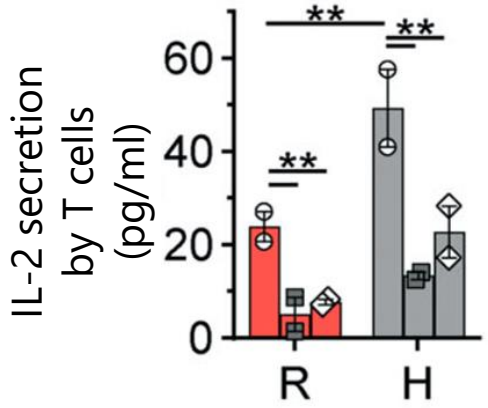
IgG forms a ternary complex with FcRn and CD32a (FcγR-IIA), a low affinity FcγR with stimulatory activity



The CD32a-R131H polymorphic variant is linked with autoimmunity and favors ternary complex formation



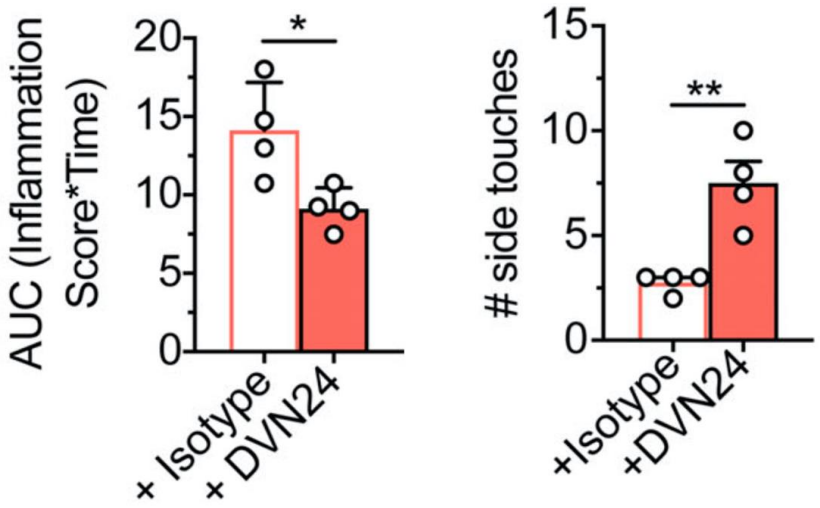
The H variant primes T cells better than the R variant and relies heavily on FcRn for this activity



Hubbard et al., *Journal of Clinical Investigation*, 2020

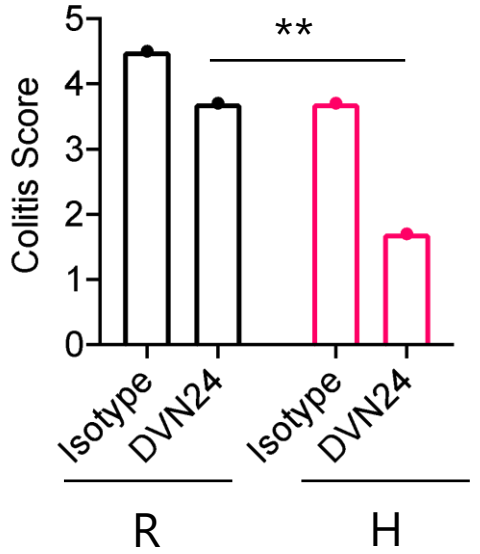
Interfering with FcRn-mediated Priming Improves Symptoms in Pre-clinical Autoimmune Disease Models

IgG IC driven arthritis improves using a regimen that doesn't decrease antibody levels



Hubbard et al., *Journal of Clinical Investigation*, 2020

Mice expressing the CD32a-H variant respond better to anti-FcRn therapy in a model of IgG driven colitis



Hubbard et al., *Gastroenterology*, 2020

Disclosure

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