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STIFEL | Healthcare

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Recent issues in case you missed and want to read: November 20, 2023 (M&A) November 13, 2023 (AHA, Bear Market) November 7, 2023 (Unmet Needs) October 30, 2023 (ADCs) October 23, 2023 (ESMO Review) October 16, 2023 (Cancer Screening) October 9, 2023 (Biosimilars, M&A) October 2, 2023 (FcRn, Antibiotics) September 25, 2023 (Target ID) September 18, 2023 (Changing Pharma Strategy) September 11, 2023 (US Health System) September 5, 2023 (FTC, IRA, Depression) August 21, 2023 (Covid, China) August 7, 2023 (Employment, Summer reading) July 24, 2023 (Alzheimer's Disease) July 7, 2023 (Biotech market review – H1 '23) July 1, 2023 (Obesity drugs) June 19, 2023 (Generative AI) June 12, 2023 (IRA, State of Industry) May 29, 2023 (Oncology update) May 22, 2023 (FTC case on Amgen/Horizon)





# Bullish on Biotech

## Stifel Healthcare: Premier Investment Banking Franchise

STIFEL | Healthcare

Our Deep Sector Knowledge and Differentiated Capabilities Drives Strong Results For Our Clients

<b>100+</b>	<b>Deep Team Covering 4 Industry Verticals</b>	<b>15</b>
Investment bankers across the	Biopharma & Spec Pharma I HCIT I Medtech & Diagnostics I	Research analysts covering <b>238</b>
U.S. and Europe <sup>(1)</sup>	Healthcare Services	companies
Bookrun <b>195</b> financings	<b>Prolific Underwriting Experience</b>	Raised <b>\$118.5bn</b> for <b>300</b>
raising over <b>\$38.9bn</b> 2020 -	IPOs I Follow-ons I CMOs I RDs   ATMs   144As   Private Placements	healthcare companies in <b>612</b>
2023YTD	PIPEs   Converts   Debt	transactions <sup>(3)</sup>
<b>147</b> Advisory transactions 2020 - 2023YTD <b>\$27.3bn</b> of value <sup>(2)</sup>	<b>Dedicated M&amp;A Franchise</b> Mergers   Acquisitions   Divestitures   Collaborations   Partnerships   Activist / Defense   Other Financial Advisory Situations	<b>360</b> transactions since 2010 <sup>(3)</sup> <b>160+</b> cross-border deals since 2010 <sup>(3)</sup>
2022 Investment Bank of the Year – Americas <sup>(4)</sup> #1 ranked bank for virtual roadshows in 2022 <sup>(5)</sup>	<b>Backed by Full Service Investment Bank</b> Research   Trading & Distribution   M&A   Equity Capital Markets   Debt Capital Markets   Restructuring Advisory   Private Capital Markets	Research-led Conferences Content driven research events

(1) Accounts for Stifel's recent acquisition of Torreya Capital LLC and its affiliated entities, which closed on March 1, 2023.

- (2) Only includes value where purchase price was disclosed.
- (3) Since Q4 2010.
- (4) Global M&A Network as of February 6, 2023.
- (5) Investor Relations magazine as of February 7, 2023.

## Stifel is a Leader in Biopharma Financings



#### Recent IPOs<sup>(1)</sup> **Recent Secondary Equity Financings Recent Alternative Financings**<sup>(2)</sup> \$575,000,000 \$120,000,000 \$100,000,000 \$250,070,000 \$345,057,500 \$220,800,000 \$185,000,000 \$150,150,000 \$517,500,000 \$100,000,000 \$80,000,000 €35,700,000 $\alpha$ tec LEXEO APOGEE inventiva IONIS 🛞 Neumora CUTERA MINERALYS 🖒 cerevel bionano Vistagen \* VIRIDIAN Private Placement & onfidentially Markete oficientially Market Convertible Royalty Certificate Convertible nitial Public Offering nitial Public Offering Initial Public Offering Senior Notes Issuance Senior Notes Initial Public Offer PIPE Follow-on Offering ollow-on Offering Registered Direct **Convertible Notes** Left Bookrunning Manager Joint Bookrunning Joint Bookrunning Joint Bookrunning Joint Bookrunning Co-Lead Joint Bookrunning Joint Bookrunning Joint Bookrunning Co-Lead Manager Manager Manager Manager Placement Agent Manager Manager Manager Placement Agent Sole Agent Co-Manage September 2023 October 2023 October 2023 June 2023 December 2022 November 2023 July 2023 February 2023 October 2023 October 2023 October 2023 August 2023 \$122,867,412 \$230,000,000 \$98,000,000 \$172,500,000 \$115,000,000 \$30,000,000 \$100,000,000 \$200,000,000 £62,000,000 \$104,500,000 \$55,300,000 \$230,000,000 PROFCUND MEDICAL INVACARE 🖰 HILLEVAX /IKING 🙆 Avacta INVAC4R CUTERA 🖰 HILLEVAX (vigil P PepGen PepGen ALSP ORCHID Convertible Bond & Follow-on Offering onfidentially Markete Senior Secured Exchange of nitial Public Offering Initial Public Offer nitial Public Offering SPAC IPO Follow-on Offering t-the-Market Offerii t-the-Market Offer t-the-Market Offerin Term Loan onvertible Notes Convertible Notes Sole Bookrunner Joint Bookrunning Manager Sole Placement Ager ole Broker and Nom Joint Bookrunnin Joint Bookrunning Left Bookrunning Joint Bookrunnin Sole Bookrunnin Manager Sole Agent Joint Agent e Placement Age Co-Lead Manager Manager Sole Agent Manager Manager Manager April 2022 January 2022 November 2021 Commenced July 2023 October 2022 July 2022 July 2022 May 2022 May 2022 September 2023 nenced September menced August 2 \$230,000,000 \$93,600,000 \$483,000,000 \$92,000,000 \$95,000,000 \$130,000,000 Up to \$40,000,000 £10.000.000 \$30.000.000 \$7,900,000,000 \$2,350,000,000 DEFINITIVE kooth 🕼 renalytix athenahealth athenahealth Mtem eliem ACUMEN SFINDLETO NEUROGENI AKARI SONENDO a pertility company of **Z** BainCapital **Z** BainCapital onvertible Bond and Senior Secured Initial Public Offer nitial Public Offeri nitial Public Offeri Initial Public Offerin PIPE Follow-on Offering PIPE Equity Placing Equity Placing Senior Notes Credit Facilities Direct Public Offering Joint Bookrunning Joint Bookrunning Joint Bookrunning Joint Bookrunning ole Financial Advisor an oint Bookrunning Co-Manager oint Lead Arrange Joint Placement Agen ole Placement Ad Joint Bookrunne Financial Advisor Manager Manager Manager Manager Sole Placement Agen Manager November 2021 October 2021 September 2021 August 2021 Pendina July 2023 July 2023 July 2023 March 2022 February 2022 February 2022 September 2022

#### We have worked on 612 completed raises since Q4 2010, of which 80%+ were bookrun and / or lead managed, raising \$118.5bn

Note: As of November 17, 2023. Deal values and dates represented are as of the announcement that the definitive agreement was signed. Stifel transactions include deals completed by Stifel, Nicolaus & Company, Incorporated and its affiliated entities and Torreya Capital LLC and its affiliated entities.

(1) Dealogic as of November 17, 2023. Any pending IPO transaction tombstones on this page are neither an offer to sell nor a solicitation of an offer to buy any of these securities. An offer may only be made by the prospectus for the offering.

(2) Includes financings other than IPOs or equity financings for public companies.

### Stifel Offers Comprehensive Advisory Services To Healthcare Clients

#### **Recent Company M&A / Advisory**

#### **Recent Licensing and Collaborations**



#### Stifel is highly bullish on the biopharma sector. We have advised on hundreds of advisory deals in the field since 2010.

Note: As of November 17, 2023. Deal values and dates represented are as of the announcement that the definitive agreement was signed. Stifel transactions include deals completed by Stifel, Nicolaus & Company, Incorporated and its affiliated entities and Torreya Capital LLC and its affiliated entities.

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# The Case for Biotech Investment

## Seven Reasons to Like Biotech as an Investment Area



#### **History**

Returns in biotech have beat the market over time

attractive now

#### **Valuations**

Valuations are highly The macroeconomic picture is shifting to favor biotech

Macro

#### Pharma

Pharma has little choice but to be a heavy acquiror of biotech

#### Demand

Growth in medical spend will accelerate as an inevitable byproduct of economic growth

#### Innovation

The pace of

biomedical

innovation is

accelerating

Medical innovation is going to change our

civilization

Civilization

We Are Shifting From Two Decades Driven by Tech Into an Extended Period that Will be Driven by the Life Sciences

The healthcare sector is already a very large part of the economy.

The "high tech" part of healthcare, particularly biotech, will continue to grow at a rate higher than the overall economy indefinitely.

We are seeing a massive acceleration of underlying innovation and ongoing growth in demand to pay for the life extension associated with such innovation.

The combined effect of these and many other innovations on life spans and the progress of human civilization will be profound.

STIFEL Healthcare

### Biotech Investment Opportunity is Still Early in Evolution

It's easy to become concerned about the financial markets for biotech. The last three years have seen multiple permutations of what can go wrong when greed and fear collide in a market that combines fast money with risky, long-duration scientific projects.

Despite an abundance of highly intelligent actors, the post-Pandemic biotech market has been more challenging than any of us would have liked as high interest rates have taken hold in the face of persistent inflation.

Many investors have abandoned the biotech marketplace despite and sentiment has hit rock bottom.

We now find ourselves at a point where the macroeconomic hurricane is moving out to sea, and it will be time for investors to return to the market, motivated by the opportunity of advancing biological innovations for the benefit of patients in profound need.

### Indeed, if there is one message we wish to leave you with it is that acceleration of innovation is going to make today's travails irrelevant.

Societal wealth coupled with the natural human demand for a long highquality life is going to drive demand for the bioscience products. This will be expressed over decades and will wash away temporal concerns that one might have about politics, budgets and the IRA.

Indeed, if one looks back to the medical world of the 1920s and 1930's – it all looks very quaint and, from today's financial perspective, small time. Likewise, decades from now, when one looks back at current circumstances the same is likely to be true. The potential financial scale and human impact of bioscience innovation is far larger than most of us might dare imagine. In fifty years no one will remember how many companies had to do a reverse merger in 2023 or how many traded below cash. To illustrate the scale of what is to come, the recent interest in obesity drugs highlights the notion that there could be a drug product that has revenue on the same scale as the largest products in our society. The day could come when GLP-1's beat the iPhone in sales and profitability. At some level, government and employer desire to throttle demand are not relevant when the average American is willing to spend \$500 a month out of pocket to achieve and maintain normal weight.\* And, by the way, it can become an issue for employees and those in power in government if they dare not reimburse drug products that change the life course of citizens and employees.

The key fundamental of the bioscience sector is the exponential growth of scientific knowledge and its application. This has been the result of a long historic Enlightenment that began with Descartes, Galileo and many other brave souls. And despite current political discourse, the main dividends of the Enlightenment lay ahead of us. Progress in the understanding of biology is going to be of primary importance to humankind. It's not about pharmaceuticals, medical devices or life sciences tools. These are industries that commercialize the products of knowledge. It's the knowledge itself that is going to change humanity.

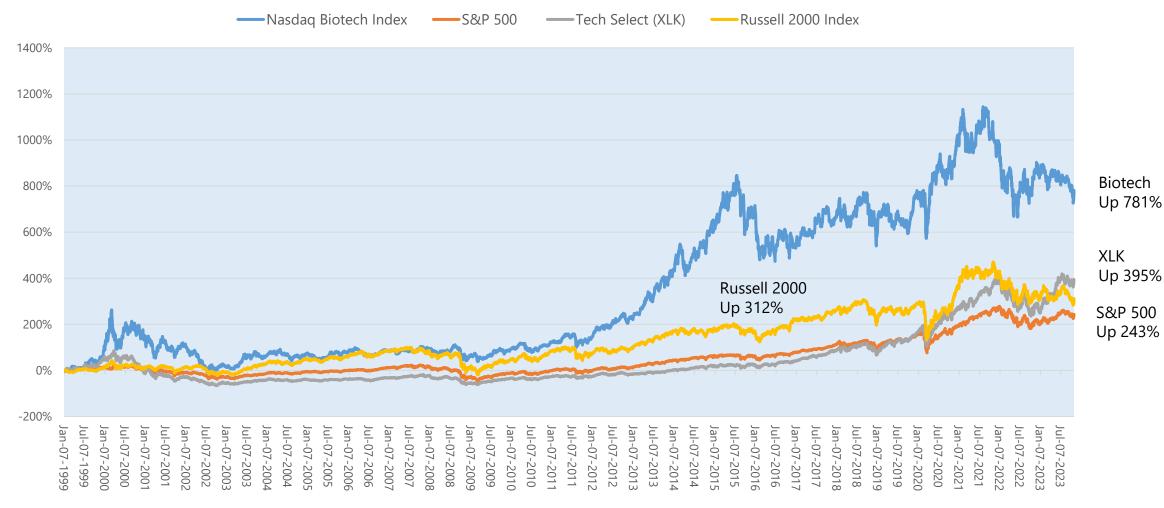
We are fortunate to live in a moment when the first gene edited drug has been approved and, in a year when decades of work on amyloid clearing and GLP-1's have led to transformative treatments for neurodegeneration and metabolic disease. Biologic innovation has been civilization changing for millennia and will continue to be for many more. The opportunities to impact human life and civilization using breakthroughs in areas like autophagy, cellular reprogramming, gene editing, immunology, incretin biology, RNA, bioelectronics, proteomics and synthetic biology remain early in their development.

# Reason 1:

# Biotech Investing Has Paid Off Before

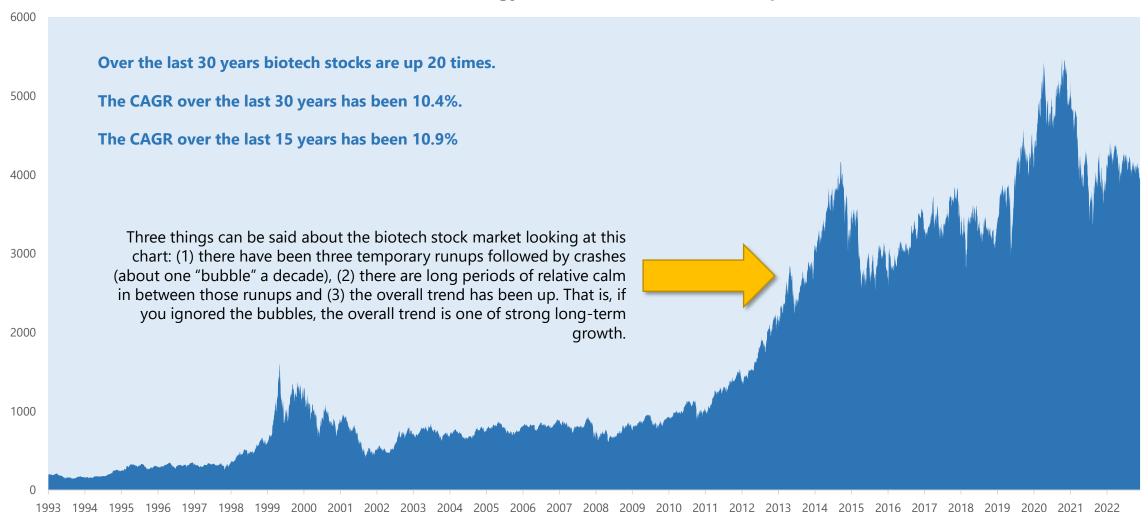
# Biotech Stocks Have Consistently Beaten Small Caps and Techs Over a Long Period of Time

NBI, S&P 500, Tech Select (XLK) and Russell 2000 Returns, Jan 1999 to Nov 3, 2023



## Biotech Up Big in Long Run

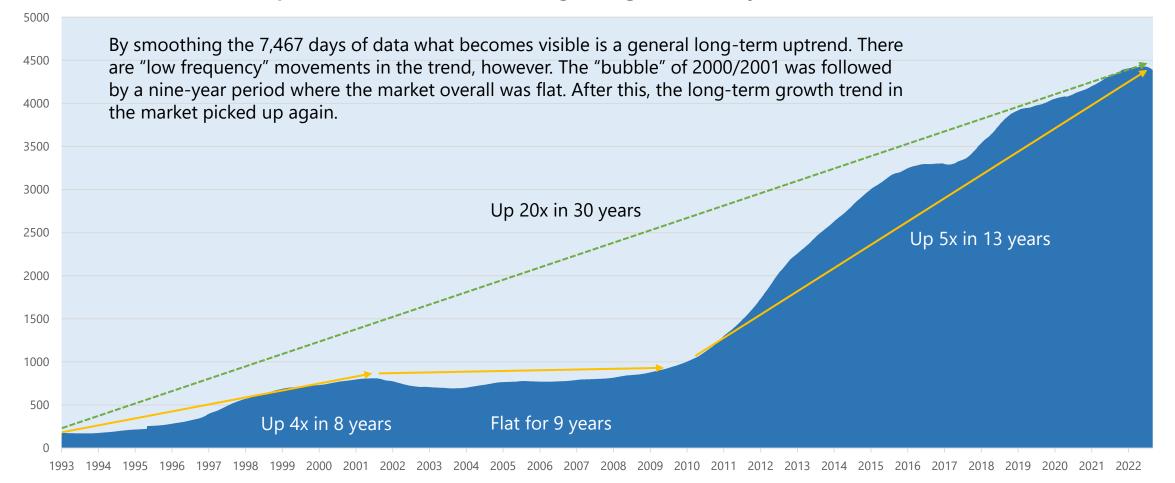
NASDAQ Biotechnology Index (NBI), Nov 1993 to Sep 30, 2023



### Smoothed Look at 30 Years of NBI Data

When one looks at the underlying market trend, it's very clear that biotech investing involves a long-term uptrend. But one must be prepared for occasional long periods of flat performance.

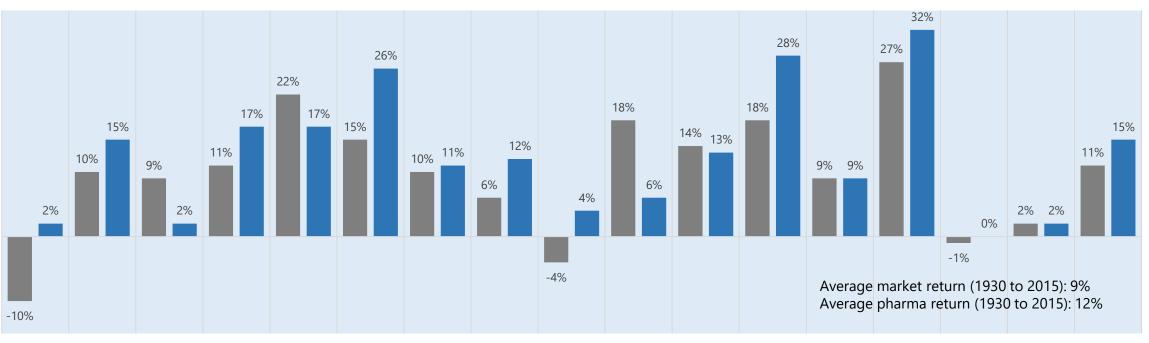
Nasdaq Biotech Index, Centered Moving Average of 1200 Days, Nov 1993 to June 2023



### If We Go Back to 1930 Does Biopharma Investment Still Win?

Between 1930 and 2015 there were 17 five-year investment periods. A portfolio of all pharma stocks beat the market portfolio in 12 of those time periods – or 70.5% of the time. Extraordinarily, even though there were three five-year time periods when one would have lost money owning a portfolio of all stocks, there was never a 5-year time period when a pharma portfolio actually lost money in the 85 years between 1930 and 2015.

Average Returns, Overall Market versus Pharmaceutical Sector, 1930 to 2015 (Thakor et.al. Study)



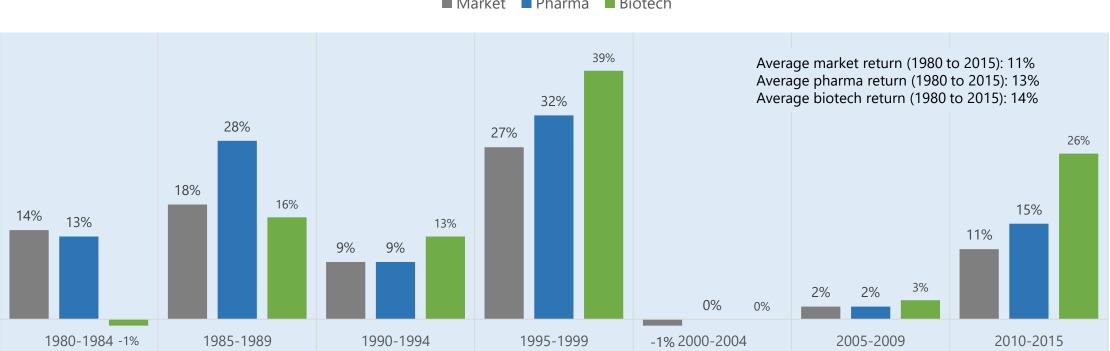
Market Pharma

1930-1934 1935-1939 1940-1944 1945-1949 1950-1954 1955-1959 1960-1964 1965-1969 1970-1974 1975-1979 1980-1984 1985-1989 1990-1994 1995-1999 2000-2004 2005-2009 2010-2015

### OK, Pharma Did Well Over Time - But How About Biotech?

Between 1980 and 2015 there were 7 five-year investment periods. *Both* biotech and pharma portfolios beat the market portfolio in 5 of the 7 time periods (71% of the time). The average return on the market in the 35 years between 1980 and 2015 was 11%. The average return on a portfolio of all pharma stocks was 13% and the average return on a portfolio of all biotech stocks in the same time period was 14%.\*

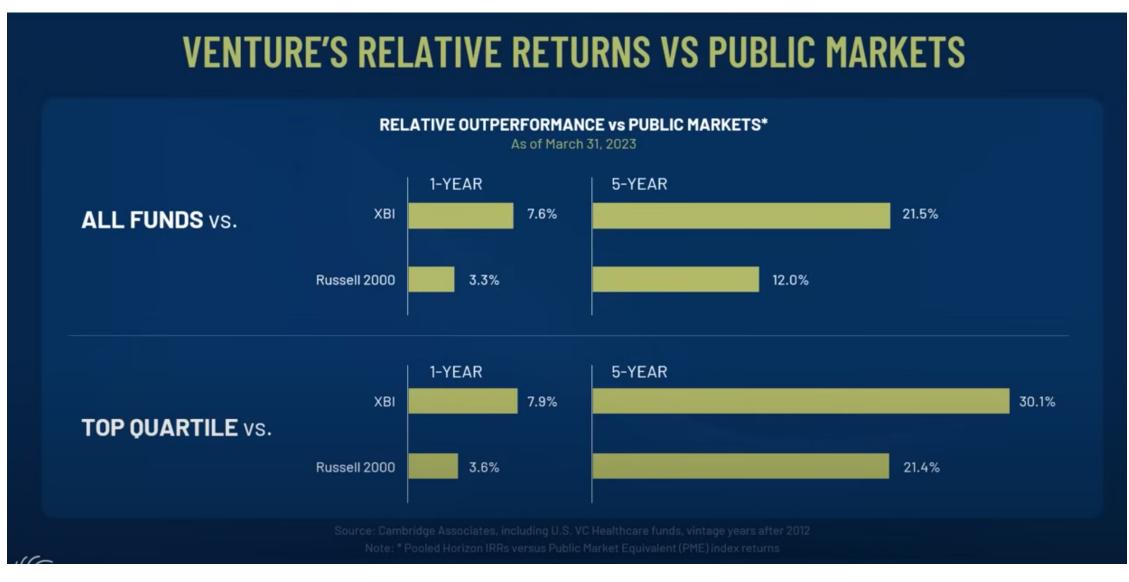
Average Returns, Overall Market versus Biotech and the Pharmaceutical Sector, 1980 to 2015 (Thakor et.al. Study)



Market Pharma Biotech

### Biotech Venture Capital Has Beaten Public Markets

This analysis from Atlas Venture's 2023 Year in Review notes that bio venture funds have handily beat public markets.



Source: https://www.youtube.com/watch?v=0DIgT32bFV4

In Many Ways Today's Biotech Sector is a Better Place to Invest Than It Might Have Been 20 Years Ago



More Sustainable Multiproduct Companies Than Before

#### Darius McDermott, FT Advisor, March 23, 2023

Importantly, the biotech sector is evolving to the point where investors could look to it as more of a core holding in the future.

In addition to blockbuster drugs, more recently we have seen the likes of advanced therapeutic modalities, such as RNA-based drugs, as well as gene and cell-based therapies investigated with a reasonable amount of success.

Back in 2018, around 80% of the industry consisted of companies with a market cap of less than \$1bn, many of which were relying on a single drug being approved to survive.

Now there is a number of large-cap lower-growth companies, which are both highly profitable and cash generative, as well as a number of mid-caps, which are either at/approaching profitability and are strong commercial entities.

#### Darius McDermott, FT Advisor, March 23, 2023

and Downturns

**Sheltered from Recessions, Depressions** 

AXA Framlington Biotech manager Linden Thomson says that alongside growth, the sector also offers a number of defensive characteristics.

She says: "Commercially they are typically less dependent on economic cycles, as there will always be a need for medicines and healthcare as well as breakthrough drugs to treat existing or new conditions.

"We are seeing this now as biopharma companies report robust quarterly financials in more challenging economic conditions."

The sector is also showing signs of maturation – making it a more attractive core holding in challenging periods. There will be major opportunities for talented active managers.

In Many Ways Today's Biotech Sector is a Better Place to Invest Than It Might Have Been 20 Years Ago



**Genetically Targeted Medicines are More Likely to Do Well** 



**R&D is Getting More Efficient – Spend Per Drug Approval is Dropping** 

We are in an area where genetics and other 'Omics technologies are informing the selection of drug target. This has led to a golden era of geneticallytargeted medicines across a wide range of modalities including ASO's, RNAi, gene therapies and antibodies.

The development success rates of drugs that have been developed based on a genetically-identified target has been systematically higher than success rates on other types of drugs.

#### Ringel et.al., Boston Consulting Group, April 16, 2020

"Early in the last decade, researchers at Sanford Bernstein published 'Eroom's Law'— Moore's Law in reverse — that the all-in cost of R&D on new drugs approved by the US FDA had risen exponentially for 60 years (Nat. Rev. Drug Discov. 11, 191–200; 2012).

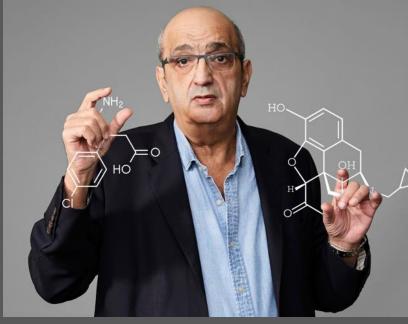
Starting around 2010, the trend line changed, with a net result of an additional 0.7 new molecular entity (NME) launches per billion US\$ of R&D spending per year by 2018."

## Ventner and Cohen Saw the Impact of the Genome in 2004



**Craig Venter** 

"If the 20th century was the century of physics, the 21st century will be the century of biology. While combustion, electricity and nuclear power defined scientific advance in the last century, the new biology of genome research—which will provide the complete genetic blueprint of a species, including the human species—will define the next."



**Daniel Cohen** 

Craig Venter and Daniel Cohen "The Century of Biology," 2004

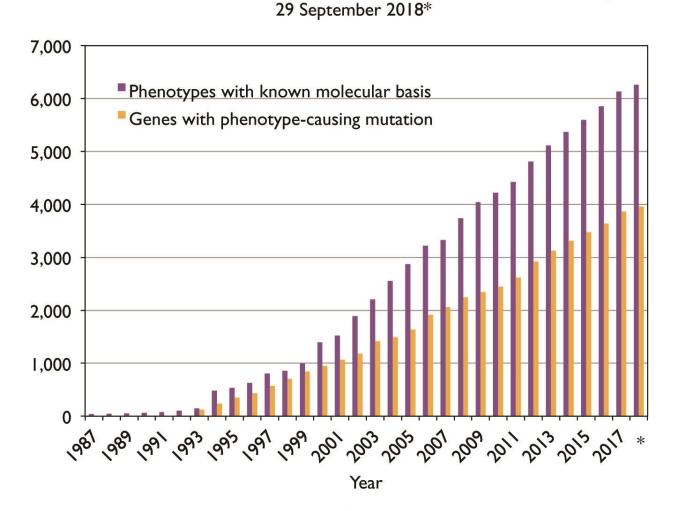
# Explosion in Understanding of Genetics and Disease

The pace of disease gene discovery as cataloged by the OMIM Morbid Map Scorecard.

The phenotype–gene relationships are tabulated in OMIM's Morbid Map of the Human Genome (Morbid Map). Currently, over 6,200 phenotypes have been attributed to molecular alterations in over 3,900 genes (Figure 1).

OMIM as of Nov 2023 lists 4,857 genes with a phenotype-causing mutation and 7,444 phenotypes with a known molecular basis.

### Growth of Gene-Phenotype Relationships



### Drug Candidates with Genetic Supporting Evidence Are 2-3 Times More Likely Than Normal to be Approved

Eric Vallabh Minikel, Jeffery L Painter, Coco Chengliang Dong and Matthew R. Nelson, "Refining the impact of genetic evidence on clinical success," *MedRxiv*, June 29, 2023.

Note: This paper looks at **RS** (the odds of a genetically-motivated drug target getting approved versus a non-genetically defined drug target). If RS=1 then the odds would be the same. In almost all cases, RS is over 2 and, for some subsets, it is over 3.

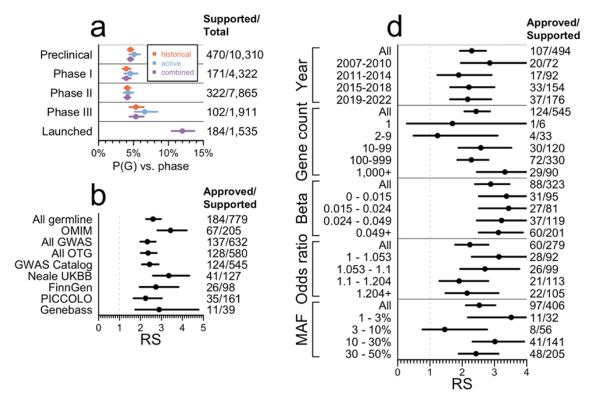


Figure 1. Impact of genetic evidence characteristics on relative success. **A)** Proportion of target-indication (T-I) pairs with genetic support, P(G), as a function of highest phase reached. Bars are Wilson 95% confidence intervals. **B)** Sensitivity of relative success (RS) from phase I launch of T-I pairs with genetic evidence to source of human genetic association. **D)** Sensitivity of RS for OTG GWAS-supported T-I pairs to binned variables: i) year in which a T-I pair first acquired human genetic support from GWAS, excluding replications and excluding T-I pairs otherwise supported by OMIM, ii) number of genes exhibiting genetic association to the same trait, iii) quartile of effect size (beta) for quantitative traits, iv) quartile of effect size (odds ratio, OR) for case/control traits standardized to be >1 (i.e., 1/OR if <1), and v) order of magnitude of minor allele frequency bins. Bars are Katz 95% confidence intervals.

# Odds of Approval of the Genetically Identified Drug Target Can Go Much Higher Than Twice Normal

King EA, Davis JW, Degner JF. Are drug targets with genetic support twice as likely to be approved? Revised estimates of the impact of genetic support for drug mechanisms on the probability of drug approval. *PLoS Genet*. 2019 Dec 12;15(12):e1008489.

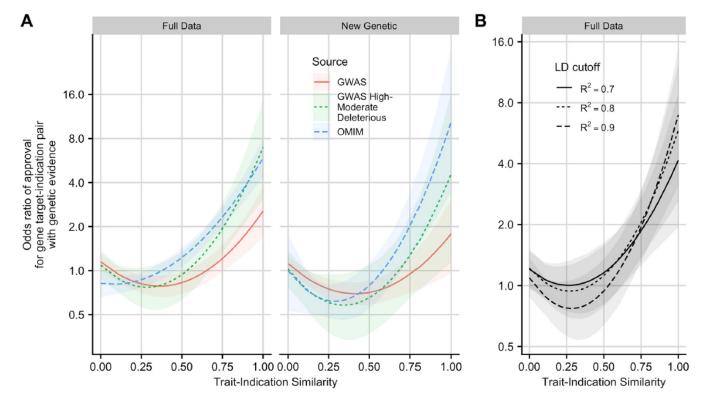


Fig 2. Estimated odds ratio of gene target-indication pair attaining approval, as a function of similarity between drug indication and the most similar trait associated with the target. A: Left: All genetic associations. Right: Only genetic associations reported after 2013 download. B: Effect of LD expansion threshold  $R^2$  on the estimated approval odds ratio of a drug gene target-indication pair supported by a GWAS high-moderate deleterious variant. Posterior median and pointwise 95% credible interval from Bayesian logistic regression.

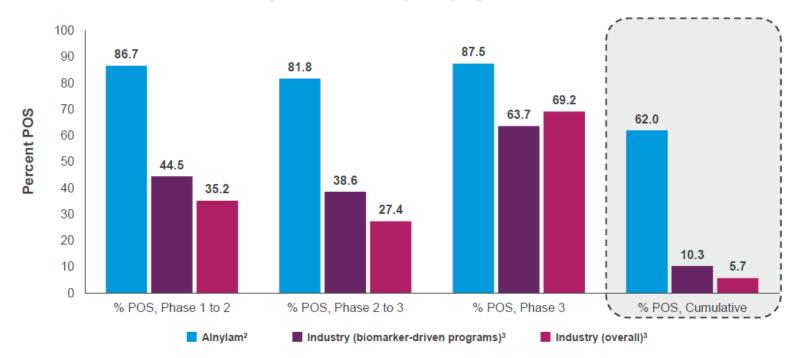
"We found strong and statistically significant positive associations between GWAS genetic evidence and drug success when considering only the highest confidence SNP-gene links, characterized as having a leading SNP with  $R^2 > 0.9$  to a variant predicted to be highly or moderately deleterious."

"Under this model, approval is positively associated with trait similarity for supporting GWAS and OMIM associations, with 95% credible intervals excluding zero (Fig 2A). When associated traits are sufficiently similar (for GWAS, roughly the similarity between Stomach Neoplasms and Colorectal Neoplasms), gene targetindication pairs with GWAS or OMIM associations are more likely to be approved."

# Example of High POS Made Possible By Genetic Targeting: Alnylam RNAi Platform

High-Yield Productivity of Alnylam RNAi Therapeutics Platform

Comparison of Historical Metrics to Alnylam Portfolio<sup>1</sup>



#### Probability of Success (POS) by Phase Transition

<sup>1</sup> Analysis as of December 2022; Past rates of Alnylam and industry respectively may not be predictive of the future

<sup>2</sup> Alnylam programs biomarker-driven at all stages of development (100%); figures include Alnylam-originated molecules now being developed by partners

<sup>3</sup> Wong et al., Biostatistics (2019) 20, 2, pp. 273-286

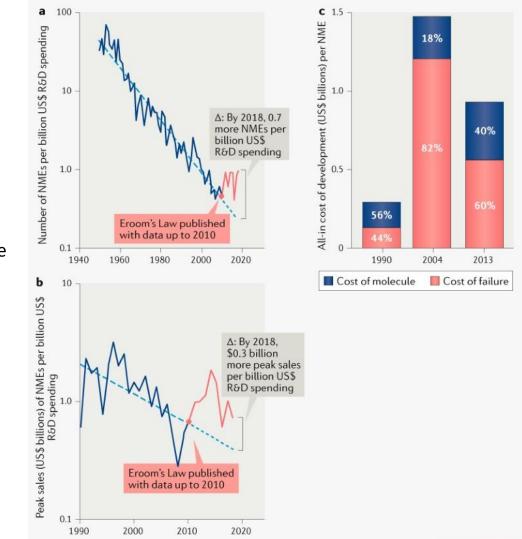
# R&D Spend Per New Drug Approval is Dropping

#### Ringel et.al., Boston Consulting Group, April 16, 2020

Early in the last decade, researchers at Sanford Bernstein published 'Eroom's Law'— Moore's Law in reverse — that the all-in cost of R&D on new drugs approved by the US FDA had risen exponentially for 60 years (Nat. Rev. Drug Discov. 11, 191–200; 2012). Among the potential contributing factors underlying the trend, the authors highlighted a progressively higher bar for improvements over existing therapies (the 'better than the Beatles' problem) and a progressive lowering of risk tolerance by regulatory agencies (the 'cautious regulator' problem). However, as the researchers posited might happen, about the same time Eroom's Law was published, it was already being broken. Here, we analyse the changes and discuss the underlying factors.

#### Breaking the law: how and why

Starting around 2010, the trend line changed, with a net result of an additional 0.7 new molecular entity (NME) launches per billion US\$ of R&D spending per year by 2018 (P <1.5 × 10–10) (Fig. 1a). This change is seen not just in the raw count but also with the value-weighted count of drugs (P <2.5 × 10–5) (Fig. 1b), which is more pertinent from both an investor and patient perspective, albeit noisier to measure (Drug Discov. Today 22, 1749–1753; 2017).



### Bottom Line

Evidence going back to the 1930s shows that the biopharmaceutical industry has been a good place to invest relative to the overall stock market.

It's well known that past performance is not necessarily predictive of future returns. Thus, we ask how investment conditions today compare to those of the past.

While, of course, we are not able to forecast future returns, we can say that there are numerous reasons to think that fundamental investment conditions today for the biopharma sector are, if anything, better than in the past.

## Reason 2:

# Valuations are Attractive Now

# We Have Spent 2023 in a Biotech Shakeout Period

# Biotech Went Through Its IPO Boom. Now the Shakeout Is Underway

Industry stock gauge has fallen for the past two years

Public debuts cooled last year after flood of new firms

By Breanna Bradham

February 13, 2023 at 1:05 PM EST

The biotech industry is in shake-out mode after the ranks of public drug developers swelled in recent years amid an IPO boom.

# There Are Still Over 200 Life Science Companies Trading Below Cash Today

Number of Negative Enterprise Value Life Sciences Companies Worldwide

11/17/2023		204	
11/10/2023		220	
11/3/2023		215	
10/27/2023		232	
10/20/2023		223	
10/13/2023		214	
10/6/2023		209	
9/29/2023		201	
9/22/2023		195	
9/15/2023		183	
9/8/2023		179	
9/1/2023		168	
8/19/2023		173	
7/21/2023		165	
6/23/2023		170	
5/26/2023		168	
4/28/2023		211	
3/24/2023		219	
2/3/2023		191	
1/13/2023		195	
12/16/2022		220	
11/18/2022		204	
10/21/2022		230	
9/23/2022		221	
8/25/2022		172	
7/29/2022		197	
6/10/2022		199	
5/11/2022		220	
4/1/2022		140	
3/25/2022		137	
2/25/2022		145	
1/1/2022		83	
12/1/2021		62	
11/1/2021		33	
10/1/2021	Source: CapitallQ	26	
9/1/2021		21	

Prior to 2021 it was rare for a biotech company to trade below cash.

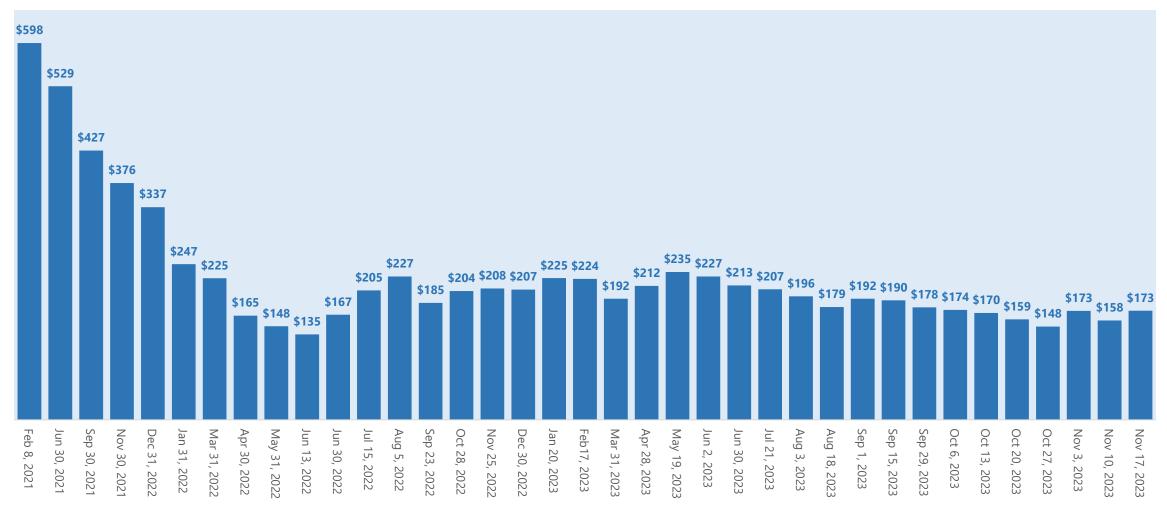
In general, when a company trades below cash it is a sign of a major value disconnect between investors and the company's management and board as it assumes that the company will destroy value. Investors are saying this company is better off dead than alive. As seen in the previous section, history tells a very different story.

In the long run, on average, biotech companies create tremendous value.

### Entire Biotech Sector is Worth Less Than 30% of Peak (Feb. 2021)

If you added up the value of every public biotech company in the world it would be \$173 billion. This is just 6% of what pharma is worth.

Total Enterprise Value of Publicly Traded Global Biotech, Feb 8, 2021 to Nov 17, 2023 (\$ Billions)



Source: CapitalIQ. Biotechs are defined as any therapeutics company without an approved product on any global stock exchange. Last week included a removal of a commercial company with a \$7bn value.

# **Rajiv Kaul of Fidelity:** Now is a Good Time to Invest in Biotech

"So, there's a lot of pain out there. And ... a long-term investment perspective is what we take here at Fidelity. We're trying to build some of the most amazing biotech companies of the future and that takes a long time and requires a lot of capital. And it's not easy to get breakthrough drugs that are transformative for patients and payors.

So, if you have that sort of mindset that you would like to stay with... I don't know if I could pick a better time [to invest in biotech]. I don't want to hype it obviously. I don't know what's going to happen in the next month, next three months or this year.

In the short-term people seem very focused on macro concerns, interest rate hikes, recession, who knows. With global macro political events there is always something to be worried about." (Jan 20, 2023)



**Rajiv Kaul** Fidelity

# **Rajiv Kaul of Fidelity:** This is a Great Environment for Stock Picking

"[W]e've seen valuations for [biotech] companies come back down to earth, coming closer to their fundamental values.

On the other hand, those companies with strong science and management teams that are able to allocate capital efficiently, should be positioned to outperform, as we're in an environment driven by stock picking, rather than sentiment." (Sep 28, 2023)



**Rajiv Kaul** Fidelity

## Sentiment is Not Good Now

In many conversations with market participants in recent months, there is an **ebbing of optimism** – the sense that this market will turn soon or is turning now.

We have heard this from many biotech CEOs and investors.

One of the effects is that investors are trigger happy on negative news.

For example, bad news recently sent Akero's stock down 70% and 89Bio instantly joined suit, even though it had no specific negative news.

Conversations with fund managers identify many groups that are "cutting back exposure" until the new year. The market is increasingly bifurcated. One observer said to us:

"The bifurcation of the haves and have nots is a key aspect of the today's biotech market and is becoming ever more evident. Sentiment remains terrible as 'have not' stocks are getting pounded into the ground while the 'haves' are struggling to just stay in place."



### Recent Sentiment-Related Quotes from Twitter

#### **Biotech Hangout Chatter, Nov 17, 2023**

"#BiotechHangout kicks off with a discussion of market sentiment. @daphnezohar notes "sentiment still seems very negative despite some good news on inflation and interest rates." @cngarabedian adds "we all remain very hopeful" and we're waiting to feel like we're out of the woods."

"Biotech is back to where it was 5 or 6 years ago. There are dozens of compelling entry points in biotech as a result of the bubble's collapse. That said, innovation is better than it's ever been and more orderly than it's ever been," argues @biotech1. @timopler heard a more negative take at the Stifel conference: "I don't think people have gotten that memo yet." "Sentiment toward biotech remains freezing."

Adam Feuerstein, Stat+, Nov 1, 2023

"It can be weird driving around a biotech hub when you see names on enormous buildings that are now penny stocks."

Brad Loncar, Head, Biotech TV, Nov 17, 2023

#### Media Stories Reinforce Biotech Gloom

These stories would leave you with the impression that biotech is set for a long-term period of depressed values.

**BIOTECH AND PHARMA** 

#### Biotech Stocks Are Rallying, but the Outlook Isn't Good

By Josh Nathan-Kazis Follow Nov 15, 2023, 12:28 pm EST

**Barron's** 

November 16, 2023 10:33 AM EST Financing, Startups

Endpoints News 📼 👱 in 🖌

Biotech's IPO outlook for the rest of the year sours in wake of war, broader industry struggles

Oct 12, 2023 - Economy

# Biotech venture capitalist says bad industry outlook will continue Axios

#### November brings new flurry of biotech layoffs Biopharma Dive

Seres Therapeutics, Kronos Bio and Rani Therapeutics joined Sangamo in announcing job cuts, while private biotech LocanaBio revealed it's shutting down.

Published Nov. 3, 2023

#### Half of biotechnology companies could disappear over the coming

#### Years Trustnet

23 October 2023

The sector is oversaturated with over-correlated companies that "shouldn't really be there," according to International Biotechnology Trust's Poszepczynski.

#### But Does Sentiment Matter?

Why should any of us care that biotech investors are in a bad mood?

Few will doubt that biotech investors today do not have a good view of the market.

There is a general view of pessimism as to how the biotech markets are going to perform.

But, why is this relevant at all? That is, shouldn't stocks perform according to their underlying fundamentals?

We raise this question simply to point out that if mood does matter then it's relevant to think about it as a factor that could be reversible without any change in fundamentals.

Further, if it matters and one is right about fundamentals then mood might actually cause fundamentals (e.g., values relative to an innovation opportunity) to not matter.

In the famous words of Franklin Delano Roosevelt at the depths of the Great Depression: "All we have to fear is fear itself."

#### Academic Research on Mood and Sentiment

Cohen-Charash Y, Scherbaum CA, Kammeyer-Mueller JD, Staw BM., "Mood and the market: can press reports of investors' mood predict stock prices?," *PLoS One,* Aug 28, 2013.

"We examined whether press reports on the collective mood of investors can predict changes in stock prices. We collected data on the use of emotion words in newspaper reports on traders' affect, coded these emotion words according to their location on an affective circumplex in terms of pleasantness and activation level, and created indices of collective mood for each trading day. Then, by using time series analyses, we examined whether these mood indices, depicting investors' emotion on a given trading day, could predict the next day's opening price of the stock market. The strongest findings showed that activated pleasant mood predicted increases in NASDAQ prices, while activated unpleasant mood predicted decreases in NASDAQ prices. We conclude that both valence and activation levels of collective mood are important in predicting trend continuation in stock prices."

Sentiment is a thing.

It can impact markets.

There is overwhelming evidence from the behavioral finance literature that investor sentiment can create local distortions in stock prices. If investors are happy and excited, stock prices tend to go up. If collective mood is negative, then the opposite is possible.

#### Mood's Impact on Stocks Tends to be Self-Correcting

Paul Tetlock, "Giving Content to Investor Sentiment: the Role of the Media in the Stock Market," *Journal of Finance*, May 8, 2007

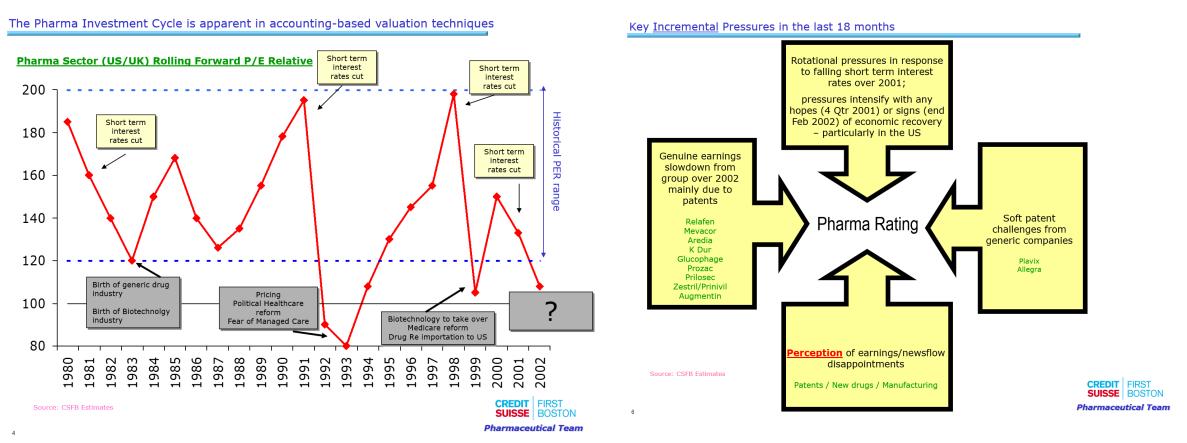
"I quantitatively measure the interactions between the media and the stock market using daily content from a popular Wall Street Journal column. I find that high media pessimism predicts downward pressure on market prices **followed by a reversion to fundamentals**, and unusually high or low pessimism predicts high market trading volume. These and similar results are consistent with theoretical models of noise and liquidity traders, and are inconsistent with theories of media content as a proxy for new information about fundamental asset values, as a proxy for market s."

The impact of bad investor sentiment on short-term market direction is well understood by academics.

In this study, Paul Tetlock showed that the impact of pessimism on markets tended to be self-correcting insofar as depressed share prices create a fundamental buying opportunity for dispassionate investors.

#### Remembering 2002 and 2003

We have been in down cycles before. In 2002 there was an environment of high rates, massive pressure on pharma earnings, patent challenges and a perception of earnings disappointments. Sentiment was dark and the thought was that the pharma industry would never recover.



#### Bruce Booth Reminds Us: What's Old is New

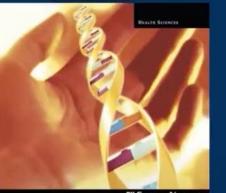
**Comments made in the E&Y Biotech Review Report of 2003 Could Have Been Made Today.** 

#### **CHALLENGING TIMES IN BIOTECH**

We lived and witnessed a phenomenon in the biotechnology arena I characterized as **gravity suspended**... **Discriminating capital allocation** is replacing the honeymoon phase of prior years.



#### Fred Frank Vice Chairman, Lehman Brothers



ERNST & YOUNG

Resilience Americas Biotechnology Report 2003



Only a few years ago the buzzwords were about **platform technologies**... Today, it is difficult even for companies with late-stage technologies and Phase II **clinical data** to receive any interest from the institutional investors who for decades have dominated this industry



Frank Baldino CEO, Cephalon

Source: Ernst & Young Resilience Americas Biotech Report 2003

#### Bruce Booth Notes Many Similarities Between Now and 20 Years Ago

### PARALLELS: 2003 & 2023



Source: https://www.youtube.com/watch?v=0DlgT32bFV4

CONTEXT

#### COMMON THEMES

- Public markets finding bottoms
- Venture funding collapsed
- ✓ IPO window closed
- Platforms out, products in
- Consolidation / M&A
- ✓ Spike in restructurings
- Bubblicious hindsight

**VENTURE ECOSYSTEM** 

Drug pricing & policy issues

43

#### **Market Rebirth:**

#### What Happened After the E&Y Resilience Report?

#### The Nasdaq Biotechnology Index



in the decade that followed.

### It's Déjà Vu All Over Again: Comments from 2016

It felt in 2016 like the biopharma industry had hit a pothole from which it could not recover.

#### "Biotech shares fall after Clinton tweet sparks selloff...

Biotechnology shares fell [dramatically] after Democratic presidential candidate Hillary Clinton's tweet about price gouging by drugmakers sent biotechnology shares lower [week of Sep. 21]. The Nasdaq's Biotechnology Index fell about 14%. Much of the selling was profit taking in a market that has rallied nearly 600% since the bull market began in 2009."

T. Rowe Price analysts

- IPO's getting pulled although a few are going through. It's obviously going to be tougher going for public equity access.
- This does not bode well for the crossover market nor for the VC market.
- As a result, we are in the most bearish period for life sciences stocks since 2009.
- We think that Medicare reforms on pricing of orphan drugs that are off patent are likely but that pricing of on-patent drugs for rare conditions will remain robust.
- Payors unlikely to unilaterally change pricing of rare disease drugs. No precedent or support in the system.
- Big Pharma not yet in bargain hunting mode on biotech. Waiting for prices to level out at a lower level. This is risky for them.
- The deal market is slowing considerably. CEO's do deals when they and their investors are *confident*.

#### Market Rebirth:

#### What Happened After the 2016 Downturn?

#### The XBI more than

# Tripled

in the five years from the trough point of 2016.

#### Bottom Line

We find ourselves today near a **low point in biotech investor sentiment**. The XBI is trading at around 70 – well down from where it has been in recent years. Investors, in general, are concerned and many are pulling out of the market. There is a fundamental explanation of what's been happening. **High interest rates** have been a negative for long duration investments like biotech. Our data would suggest that **sentiment** is also playing a role. Many market events and observations are hard to explain with any fundamental story linked to interest rates. Importantly, the research shows that **negative sentiment tends to be self correcting**. It can only stay down for so long in the face of improving fundamentals. And improve they have. As noted in the next section, employment pressure on prices is easing and inflation has been falling in recent months.

#### Reason 3:

### Improving Macro Picture

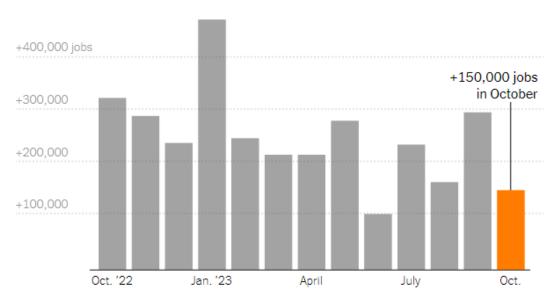
#### Macro Picture is Now Favorable For Biotech

We have gone from a world where macro was a massive headwind to biotech investors to one where it is turning into a tailwind.

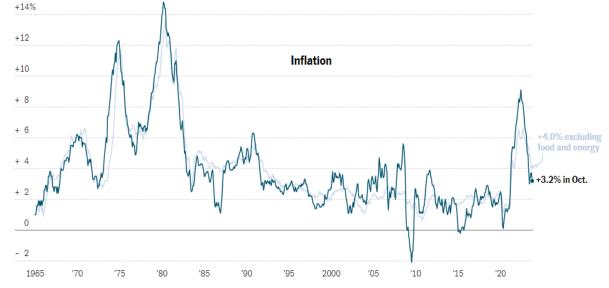
U.S. Jobs Growth in Slowing Down: This is What the Fed Wants



U.S. Inflation is Also Slowing Down: Further Good News for the Fed



Note: Data is seasonally adjusted. • Source: Bureau of Labor Statistics • By Ella Koeze



Year-over-year change in the Consumer Price Index 🔹 Source: Bureau of Labor Statistics 🔹 By Karl Russell

#### Monthly change in jobs

### ECONOMISTS STRUGGLE TO COME TO TERMS WITH "IMMACULATE DISINFLATION"

Experts said that inflation couldn't be conquered without a lot more economic pain, but it's happening.



In January of this year, when the *Journal* carried out its next survey, economists were still predicting a recession and job cuts. "For 2023 as a whole, economists expect that payrolls will decline by 7,000 a month on average," the paper reported. These predictions couldn't have been more wrong. About the only thing the economists got right was that inflation would continue to fall, but even there they underestimated the pace of decline. Earlier this week, the Labor Department reported that the consumer-price inflation fell to 3.2% in October, reversing a slight pickup over the summer. And with gas prices still falling, it seems perfectly possible that the the November figure for consumer-price inflation could begin with a two.

Taken together, these figures show that the American economy has greatly outperformed expectations over the past year, shocking some of those who argued that a big slowdown and higher unemployment would be required to break the back of inflation. "The US combination of strong growth, low unemployment and falling inflation looks rather like the 'immaculate disinflation,' in which I, for one, disbelieved," Martin Wolf, the *Financial Times*' chief economics commentator, wrote last week. Even the former Treasury Secretary Larry Summers, who is now a professor at Harvard and said last year that it would likely take an unemployment rate of 6% to "significantly restrain inflation," has rowed back a bit. "Given how strong the economy has been, there's still a surprise in what's happened to inflation," Summers told Bloomberg earlier this week.

To be fair to the inflation hawks, the immaculate disinflation that Wolf referred to has no precedent in recent history, and it has also surprised policymakers at the Fed. At their December, 2022, meeting, Jerome Powell and his colleagues predicted G.D.P. growth of just 0.5% in 2023 and an unemployment rate of 4.6% in the October-to-December quarter. Both of these predictions were way off, but in a good way.

The debate will go on, as will the parallel discussion about why, according to opinion polls, most ordinary Americans think that the U.S. economy is doing badly, and give Joe Biden negative ratings on this front. But the fact that many people are still bummed about the price of groceries and the level of mortgage rates shouldn't be allowed to obscure what is shaping up as a historic victory over inflation. That's where we are, and it's worth a holiday toast.

### Fed Hiking Cycle Looks Done After US Jobs Report Shows Cooling

#### Steve Matthews, Bloomberg, Nov 3, 2023

A cooling US job market gives the Federal Reserve room to keep interest rates on hold in December and reinforces market views that the US central bank is done with the most aggressive hiking campaign in four decades.

Nonfarm payrolls increased 150,000 last month, less than expected, following a downwardly revised 297,000 advance in September, a Bureau of Labor Statistics report showed Friday. The unemployment rate climbed to 3.9%, and monthly wage growth slowed.

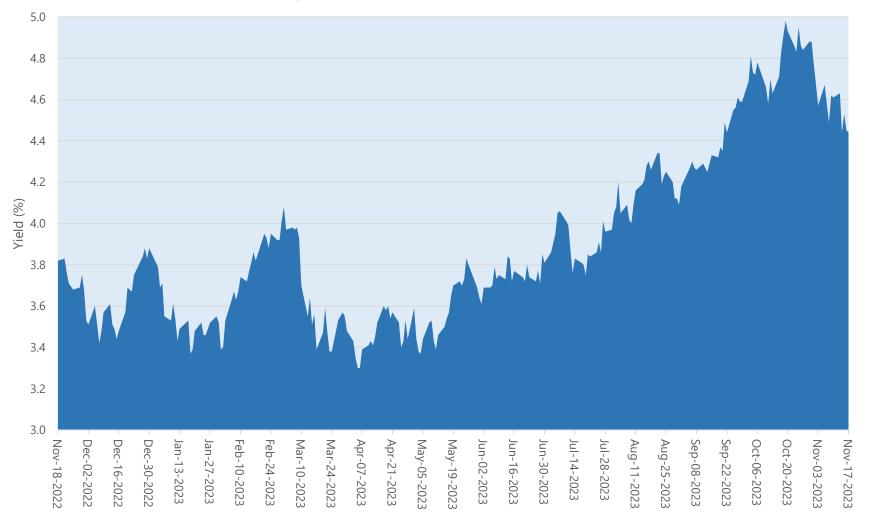
"Put a fork in it – they are done," said Jay Bryson, Wells Fargo & Co. chief economist. "If you are an FOMC official, this is what you wanted to see. This is very good news for the Fed."

The US central bank's policy-setting Federal Open Market Committee voted on Wednesday to hold interest rates at a 22-year high for a second straight meeting. Fed Chair Jerome Powell told reporters in a press briefing that it's an open question whether the central bank would need to hike again, and that it's "proceeding carefully," an assessment that's often suggested a reluctance to raise rates in the near term.



#### Big Climb in Long Treasury Yields Has Reversed

United States Treasury 10 Year Bond Yield, Nov 18, 2022 to Nov 17, 2023



Ten-Year US Treasury Bond Yields have dropped by over 50 basis points since peaking a month ago.

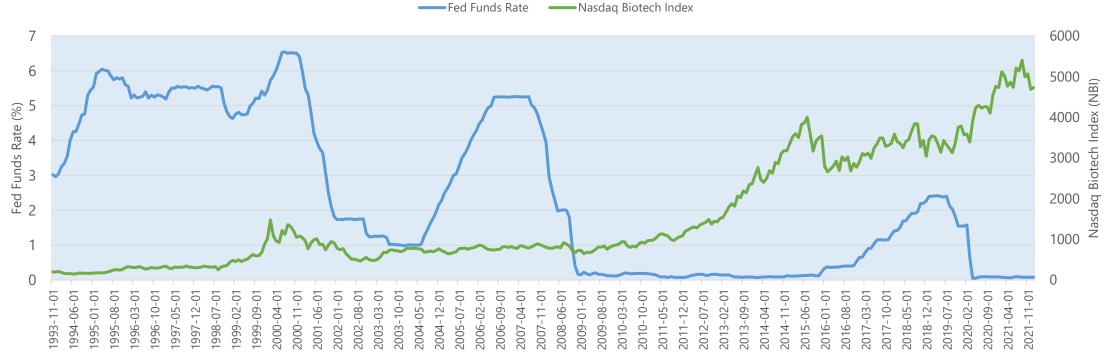
That's a huge move and a big positive for biotech.

### Important to Recall that Biotech Typically Recovers Well Before Fed Easing Begins

On average, since 1994 the Nasdaq Biotech Index (NBI) has gone up 68% of the time.

Only four of the last 28 years have seen the Fed initiate a tightening cycle, marked by an increase in Fed Funds.

The NBI rose by year end in **three of those four years** (75%). Current negative market conditions could easily reverse before the Fed begins to reduce rates in 2024.



Fed Funds Rate versus Nasdaq Biotech Index, 1993 to 2021

Source: Fed Funds rate from FRED, Federal Reserve Bank of St. Louis. NASDAQ Biotech Index from CapitalIQ.

Unemployment Rate In United States

3.9%

### High

Likelihood that the Fed will reduce the discount rate in the next six months

> In many ways, we find ourselves in a "Goldilocks" moment in U.S. economic history.

> > 0.000001

Covid-19 U.S. death rate last week Lowest since the Pandemic began

CPI Inflation Rate, US (Lowest in 2 years)

Illustration from Getty Images.

#### Reason 4:

### Pharma Needs to Acquire Biotechs

#### Continual Change in Big Pharma Industry

The list of the top 15 big pharmas of 1974 is barely recognizable today, containing only 6 companies that remain independent. The ranks of the top players in the industry are highly dynamic as the advent of new products and modalities, together with patent expiries on the old, drive dramatic change. Also notable is the decline in the EU pharma sector – once the source of most industry sales. Noteworthy is the industry's massive long-term growth (6% revenue growth after inflation, on average since 1974 – far above GDP growth).

#### **Top 15 Pharma Players Ranked by Revenue \$mm, 1974-2027**

1974		1988		2005		2014		2022		2027 (est.)	
Company	Revenue (\$mm)	Company	Revenue (\$mm)	Company	Revenue (\$mm)	Company	Revenue (\$mm)	Company	Revenue (\$mm)	Company	Revenue (\$mm)
Roche	\$1,386	Merck	\$4,984	Pfizer	\$44,280	Novartis	\$53,717	Pfizer	\$92,951	Merck	\$72,550
Merck	\$1,197	Glaxo	\$4,213	GlaxoSmithKline	\$33,960	Pfizer	\$49,605	Merck	\$57,869	Pfizer	\$68,900
Hoechst	\$1,174	Hoechst	\$3,868	Sanofi-Aventis	\$32,340	Sanofi	\$41,287	AbbVie	\$53,729	AbbVie	\$60,770
Ciba-Geigy	\$1,063	Bayer	\$3,628	Novartis	\$24,960	Roche	\$40,129	Novartis	\$52,222	Sanofi	\$60,100
Bayer	\$862	Ciba-Geigy	\$3,466	AstraZeneca	\$23,950	Merck	\$36,042	Sanofi	\$50,194	AstraZeneca	\$59,600
Sandoz	\$847	American Home Products	\$3,218	Johnson & Johnson	\$22,320	Johnson & Johnson	\$32,213	Roche	\$50,013	Novartis	\$59,390
Eli Lilly	\$789	Sandoz	\$3,089	Merck	\$22,010	GlaxoSmithKline	\$28,939	Bristol-Myers Squibb	\$45,848	Eli Lilly	\$55,940
American Home Products	\$758	Takeda	\$3,076	Wyeth	\$15,320	AstraZeneca	\$26,095	Johnson & Johnson	\$45,572	Novo Nordisk	\$53,880
Pfizer	\$740	Eli Lilly	\$2,680	Bristol-Myers Squibb	\$15,250	Gilead Sciences	\$24,890	AstraZeneca	\$43,840	Johnson & Johnson	\$51,000
Upjohn	\$683	Abbott	\$2,599	Eli Lilly	\$14,650	Amgen	\$20,063	GlaxoSmithKline	\$32,818	Roche	\$50,000
Warner-Lambert	\$611	Pfizer	\$2,539	Abbott	\$12,900	AbbVie	\$19,960	Takeda	\$30,297	Bristol-Myers Squibb	\$47,900
Rhone-Poulenc	\$595	Warner Lambert	\$2,509	Roche	\$12,900	Eli Lilly	\$19,616	Eli Lilly	\$27,691	GlaxoSmithKline	\$44,280
Sterling	\$566	Bristol-Myers	\$2,509	Amgen	\$12,020	Bristol-Myers Squibb	\$15,879	Gilead	\$27,483	Amgen	\$32,680
Abbott	\$551	Eastman Kodak	\$2,500	Boehringer-Ingelheim	\$10,840	Novo Nordisk	\$14,434	Novo Nordisk	\$27,459	Gilead	\$29,770
Boehringer-Ingelheim	\$506	Roche	\$2,365	Takeda	\$8,530	Boeheringer Ingelheim	\$13,424	Amgen	\$26,190	Takeda	\$27,650
Sales of Top 15	\$12,328	Sales of Top 15	\$47,243	Sales of Top 15	\$306,230	Sales of Top 15	\$436,292	Sales of Top 15	\$664,177	Sales of Top 15	\$774,410
Sales in 2023 dollars	\$77,419	Sales in 2023 dollars	\$123,638	Sales in 2023 dollars	\$426,048	Sales in 2023 dollars	\$570,663	Sales in 2023 dollars	\$702,525	Sales in 2023 dollars	\$819,123

**Sources**: CapitallQ and 2022 Torreya Pharma 1000 report data for 2014 to 2022 period. Harvard Business School for 1974 to 2005 data (see <a href="https://www.hbs.edu/ris/Publication%20Files/09-118.pdf">https://www.hbs.edu/ris/Publication%20Files/09-118.pdf</a>). CapitallQ analyst consensus average revenue estimates taken for 2027 revenue except for J&J and Roche where analyst reports were analyzed to take the pharma division revenue estimate average for 2027. U.S. CPI index used to inflation adjust numbers to 2023 (<a href="https://www.minneapolisfed.org/about-us/monetary-policy/inflation-calculator/consumer-price-index-1913-">https://www.minneapolisfed.org/about-us/monetary-policy/inflation-calculator/consumer-price-index-1913-</a>).

### There are Many Pharma Patent Expiries Coming Up

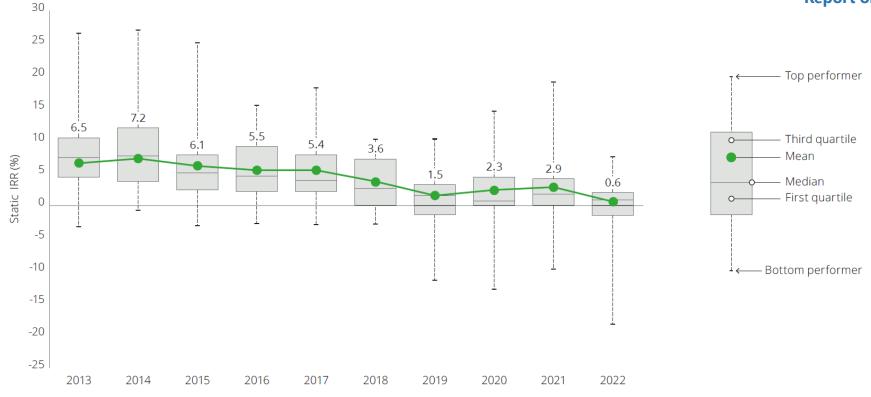
Notable LOEs through 2028

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)	U NOVARTIS	Entresto (\$7B)	@Pfizer	Eliquis (\$15B)	S MERCK	Keytruda (\$30B)
Johnson-Johnsor	Stelara (\$10B)	AstraZeneca	Brilinta (\$1.4B)	de Bristol Myers Squibb	Yervoy (\$3B)		Cabometyx (\$1B)	abbvie 🕼	Imbruvica (\$12B)	( <sup>(  </sup> Bristol Myers Squib	Opdivo (\$13B)
🤌 Jazz Pharmaceutica	is Xyrem (\$1B)	Jety BAYER	Xarelto (\$3B)	<b>P</b> fizer	Xeljanz (\$2B)	( <sup>III)</sup> Bristol Myers Squi	Pomalyst (\$2.5B)	<b>Pfizer</b>	• Ibrance (\$9B)	AMGEN	Otezla (\$3B)
Biogen	Tysabri (\$1.9B)	novo nordisk	Victoza (\$1.3B)	AMGEN	Prolia / Xjeva (\$6B)	S MERCK	Januvia / Janumet (\$1B)	Lilly	Trulicity (\$8B)	GSK	Tivicay (\$4.5B)
Sunovion	Latuda (\$2B)					Roche	Perjeta (\$5.5B)				
<b>b</b> novartis	Gilenya (\$1.6B)										
Takeda	Vyvanse (\$3.4B)										
Total 'At-Risk Revenue:	~\$41B		~\$16B		~\$14B		~\$17B		~\$44B		~\$50В

#### Big Pharma R&D Returns are Close to Zero

#### Figure 3. Return on late-stage pipeline, 2013-22, without EUA assets

Deloitte. Report on pharma innovation, Jan 2023



Source: Deloitte analysis, 2022.

Please note: 2013-2019 data includes the 15 companies of the combined cohort; 2020-2022 data includes the results of the top 20 companies by 2019 R&D spend. See appendix 2 for the data of each cohort. Compared to last year's report 2020 and 2021 figures have been restated to include the top 20 companies by R&D spend as of 2020.

"Last year we witnessed a notable rise in IRR to 6.8%, driven by forecasted high-value COVID-19 assets (including vaccines and treatments) and one high-value late-stage neurological asset that has subsequently underperformed post-launch and is no longer seeking approval beyond the FDA. As some of these assets have moved into the commercial portfolio, the IRR has declined to 1.2%. This is driven by the successful approvals of high-value forecasted assets that have been commercialized and therefore left the scope of our analysis."

Historically Big Pharma Have Gone Outside to Get Drugs

## Investigating the origins of recent pharmaceutical innovation

Alexander Schuhmacher, Markus Hinder, Alexander Dodel, Oliver Gassmann & Dominik Hartl, Nature Reviews Drug Discovery, July 5, 2023

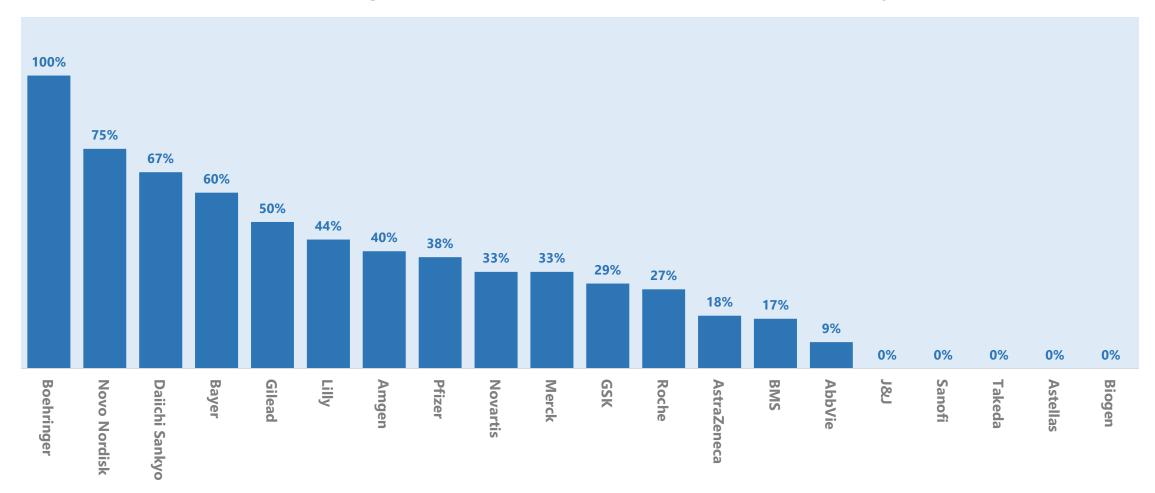
Total (138 drugs) а Collaboration -Other Internal External 28% 5% 2% **Biologics (48 drugs)** 6% 63% 27% Small molecules (90 drugs) С 44% 39% 6% 4% 3% 3% Pharma Biotech Collaboration Other academic Universities Other entities

"The FDA approved 323 new drugs between 2015–2021, of which 138 were filed for approval by the top 20 biopharma companies. The majority (65%) of these new drugs originated from external sources, whilst 28% were invented internally."

41% of approvals were from M&A and 25% were from licensing.

#### Percent of New Drug Approvals in 2015 to 2021 That Were Internally Invented

Percent of New Drug Approvals From 2015 to 2021 That Were Internally Invented



### Pharmas With Major Earnings Misses or Down Guidance in Recent Months

We have seen eventful earnings reports in recent weeks as many pharmas struggle with the current environment.

#### Sanofi shares fall 19% after cut to profit outlook

French pharma group announces consumer unit split and increased R&D investment



BMS Reports Q2 Sales Miss Amid Generic Competition, Lowers Full-Year Guidance

Published: Jul 27, 2023 By Kate Goodwin



Takeda Reports \$770M Write-Down, Cuts Profit Forecast by 71% for FY2023

Published: Oct 26, 2023 By Kate Goodwin



HEALTH AND SCIENCE

#### Pfizer slashes full-year earnings and revenue guidance as Covid treatment, vaccine sales slump

PUBLISHED FRI, OCT 13 2023-5:47 PM EDT | UPDATED MON, OCT 16 2023-9:53 AM EDT

### Matt Gline on Big Pharma Condition

"There's a major cataclysmic set of changes happening basically at all of these large pharma companies.

All of this is happening against the backdrop of trying to manufacture their growth story for the next decade."



Matt Gline CEO, Roivant Sciences

### Pharma Using M&A to Replace Upcoming Patent Expiries

Company	Core Focus Today	Key LOEs (TA)	\$M Size of LOEs	R&D Focus by TA	Recent >\$1B M&A	
Lilly	CVMB, Oncology	Cyramza (Oncology), Trulicity (CVMB), Jardiance (CVMB)	\$12,000	CVMB, Oncology	Dice Therapeutics (Immunology - \$2.4B)	
novo nordisk	сумв	Victoza (CVMB)	\$3,000	CVMB	N/A	
Johnson&Johnson	I&I, Oncology	Stelara (I&I), Xarelto (Hematology), Imbruvica (Oncology), Opsumit (CV), Prezista (ID)	\$22,250	Oncology, I&I	N/A	
abbvie	I&I, Oncology, Aesthetics	Humira (I&I), Imbruvica (Oncology)	\$27,000	Oncology	N/A	
S MERCK	Oncology	Keytruda (Oncology), Gardasil / Gardasil 9 (Vaccines), Januvia / Janumet (CVMB)	\$40,000	Oncology	Prometheus Biosciences (Immunology - \$10.8B), Imago Biosciences (Hematology - \$1.0B)	
Roche	Oncology, Neuro, I&I	Perjeta (Oncology), Tecentriq (Oncology)	\$10,500	Oncology, Neuroscience	N/A	
<b>U</b> NOVARTIS	I&I, CVMB, Hematology	Glineya (Neuro), Entresto (CVMB), Promacta (Hematology)	\$10,000	Oncology, I&I	Chinook Therapeutics (Rare Disease - \$3.28)	
AstraZeneca	Oncology, CVRM	Brilinta (CVMB), Soliris (Rare Disease)	\$4,100	Oncology, I&I, CVMB	CinCor Pharma (CVMB - \$1.8B), TeneoTwo (Oncology - \$1.3B)	
AMGEN	18,1	Prolia / Xjeva (Bone), Otezla (I&I), Krypolis (Oncology), Aranesp (CVRM)	\$12,000	Oncology, I&I	Horizon Therapeutics (Immunology - \$26.9B), ChemoCentryx (Immunology - \$3.5B)	
<b>P</b> fizer	COVID, Hematology, Oncology, I&I	Prevnar / Prevenar 13 (Vaccines), Xeljanz (1&1), Eliquis (Hematology), Inlyta (Oncology), Xtandi (Oncology), Ibrance (Oncology)	\$27,700 Oncology, Vaccines		SeaGen (Oncology - \$43.0B), Biohaven (CNS - \$11.0B), Global Blood Therapeutics (Hematology / Rare Disease - \$4.7B)	
SANOFI	I&I, Vaccines, Rare Disease	N/A	N/A	Oncology, I&I	Provention Bio (CVMB - \$2.9B)	
( <sup>III</sup> Bristol Myers Squibb	Hematology, Oncology	Yervoy (Oncology), Pomalyst (Oncology), Eliquis (Hematology), Opdivo (Oncology)	\$26,000	Oncology	Turning Point Therapeutics (Oncology - \$2.9B)	

#### Over \$500 Billion of M&A Firepower at Top 18 Pharmas

#### We define comfortable firepower as the amount of debt a company can take on given current EBITDA to arrive at a ratio of net debt to EBITDA of three times. Stretched firepower would take a company to a ratio of net debt / EBITDA of five times.

M&A Firepower of Top 16 Pharmas, November 2023 (\$ Billions)

Comfortable Firepower Stretch Firepower

This chart shows firepower of top companies. Historically, some companies like AZ and Takeda have been willing to go well beyond the 3X net debt / EBITDA comfort levels. In contrast, J&J and Roche have been reluctant to use obvious balance sheet capacity to be fully prepared for industry rainy days. Today, there is \$1.1 trillion of stretch firepower and \$521 billion of comfortable firepower among the top 18 companies listed here. In October 2020, in contrast, there was \$411 billion of comfortable firepower. Balance sheets have strengthened significantly during the Pandemic period when M&A was slow. These numbers do not adjust for Pfizer's spend for Seagen. These numbers understate firepower insofar as companies can use their equity in M&A and can gain firepower if the target has positive cash flow.



\$169

\$99

\$107

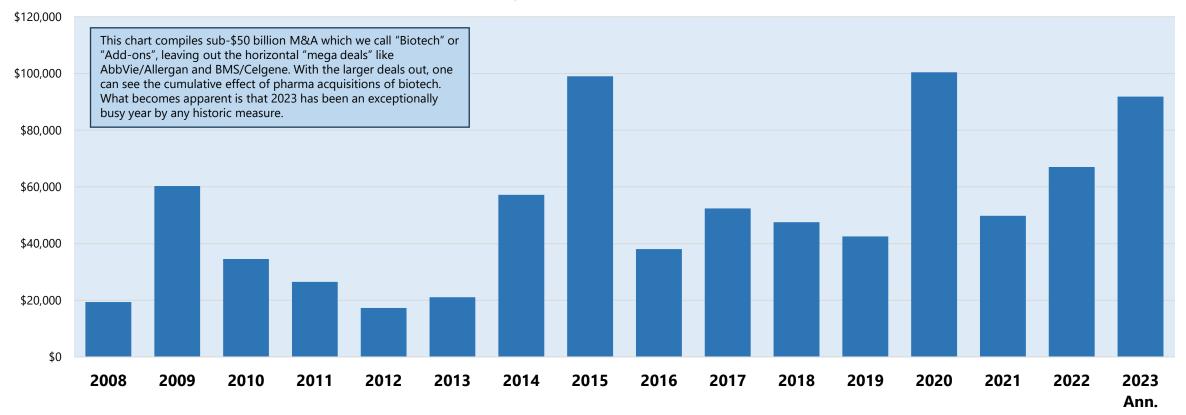
\$96

\$92

#### Big Pharma Biotech M&A Volume Exceptional in 2023

Big pharma biotech acquisition volume in 2023 was near record levels despite IRA/FTC Uncertainties. We expect to see high M&A volume continue (and, potentially, increase) in 2024.

#### Volume of Biopharma M&A Transactions by a Big Pharma Buyer with \$50mm to \$50 Billion in Upfront Payments, 2008 to 2023



#### Predictions of What We Expect in 2024 in M&A

- High M&A volume in novel therapeutics for cardiometabolic disease
- -Continuing trends from 2023
- -Big areas are obesity, heart failure, liver disease, insulin resistance
- -High interest in small molecules, orals, antibodies, peptides and nucleic acid therapies
- -In liver disease the focus is on disease modifying therapies that go beyond lipid control
- High M&A continued volume in novel therapeutics for immunology
- -Highest interest in B-cells, FcRn, eosinophils, T-cell system
- -Focus highest on first-in-class or early-in-class targets
- High M&A volume in **targeted oncology** likely
- -ADC's and immune cell engagers (particularly companies with novel targets and differentiated platforms)
- -Radiopharmaceuticals (particularly companies with manufacturing solutions)
- -Hard targets and precision oncology
- -Anything with exceptional efficacy in an area of unmet need.
- -Limited interest in IO antibodies, biologics and cell therapies these need to past the POC point to garner high interest.
- Medium M&A volume in novel therapeutics for genetic disease and neurologic disease expected
- -High interest in novel therapies for neurologic disease
- -Perennial interest in breakthroughs in diseases like Huntington's and Parkinson's
- $-{\rm Key}$  modalities include gene therapy, RNAi, mRNA, protein degradation
- -Solid volume in novel therapeutics in areas such as eye, psychiatry, endocrinology, kidney and pain
- -Late-stage assets with differentiation and outstanding efficacy against real medical need always in demand.

M&A interest is expected to be highest in cardiometabolic disease, immunology, oncology, genetic disease and neurologic diseases. Buyers have a strong preference for differentiated, late-stage assets with long-term exclusivity potential.

### What We Expect to See in 2024 by Pharma Company

17	Firm	Market Cap (\$bn)	Comfortable Firepower (\$bn)	Expected M&A Level in 2024	_Key Focus Areas	Key Driver of M&A	Size Appetite	Stage
12	Eli Lilly	\$538	\$16	High	CVM, Oncology, Neuro, Gene	Long-Term Growth	\$1bn to \$10bn	Clinical
	Novo Nordisk	\$442	\$46	High	CVM, Endocrinology, Rare	Diabetes/obesity needs	\$100mm to \$3bn	All Stages
	Johnson & Johnson	\$354	\$99	Very High	Oncology, Immuno, Neuro, CVM	Multiple LOE's	\$100mm to \$50bn	Clinical
	Merck	\$257	\$13	High	Oncology, CVM, Imm, Neuro	Keytruda LOE	\$1bn to \$10bn	Clinical
pharmas	AbbVie	\$245	\$36	Medium	Immunology, Oncology, Aesthetics	Build imm & oncology	\$100mm to \$30bn	Clinical
expected to	Roche	\$211	\$56	Medium	Oncology, CVM, Neuro, Imm, Rare	Recharge Growth	\$100mm to \$3bn	All Stages
have "high" or	AstraZeneca	\$191	\$32	High	Oncology, CVM, Immunology, Rare	Long-Term Growth	\$100mm to \$30bn	Clinical
"very high"	Novartis	\$191	\$52	Very High	Oncology, CVM, Immunology, Heme	Entresto, Cosentyx LOEs	\$100mm to \$30bn	Mid to Late
, ,	Pfizer	\$166	\$22	Medium	Immunology, Oncology, Metabolic	Multiple LOE's	\$100mm to \$3bn	Late Stage
M&A appetite	Amgen	\$143	\$14	High	Oncology, Immunology, CVM, PCP	Prolia, Otezla LOEs	\$100mm to \$20bn	Clinical
in 2024.	Boehringer Ingelheim	\$120	\$25	Low	Oncology, CNS	Long-Term Growth	\$100 to \$500mm	Early Stage
	Sanofi	\$114	\$29	Very High	Immunology, Oncology, Vaccines	Recharge Growth	\$100mm to \$20bn	Late Stage
	Bristol-Myers Squibb	\$103	\$23	Very High	Oncology, Heme, Immunology, CVM	Eliquis LOE/IRA	\$100mm to \$30bn	All Stages
	Vertex Pharma	\$96	\$25	Medium	Genetic Medicine, CNS	Disease Innovation	\$100mm to \$3bn	All Stages
	Gilead Sciences	\$95	\$18	High	Oncology, Virology, Immunology	Oncology Ambitions	\$100mm to \$10bn	Clinical
	Regeneron	\$85	\$22	Low	Oncology, CVM	Great Values	\$100mm to \$1bn	Early Stage
	Merck KGaA	\$69	\$10	Medium	Oncology, Immunology	Pharma Critical Mass	\$100mm to \$3bn	All Stages
	GSK	\$69	\$16	High	Oncology, Respiratory, ID, Vaccines	Recharge Growth	\$100mm to \$10bn	Late Stage
	Daiichi Sankyo	\$52	\$7	Medium	Oncology, White Space	Long-Term Growth	\$100mm to \$4bn	All Stages
	Takeda	\$43	None	Medium	Oncology	Oncology LOEs	\$100mm to \$1bn	All Stages
	Bayer	\$42	None	Low	Oncology, CVM, New Modalities	Pharma Critical Mass	\$100 to \$500mm	All Stages
	Sun Pharma	\$34	\$6	Medium	Dermatology, Ophtha, White Space	Branded Business Build	\$100mm to \$2bn	Late Stage
	Biogen	\$33	\$2	Medium	Immunology, Rare, Neuro	Rebuild Growth Story	\$100mm to \$2bn	Clinical
	Astellas	\$21	\$2	Medium	Immune-Oncology, Ophtha	Xtandi LOE	\$100mm to \$3bn	Mid to Late
	Otsuka	\$20	\$10	High	Neuro, Nephrology, Rare	Build R&D Capacity	\$100mm to \$3bn	All Stages

Source: Stifel IB analysis

#### Bottom Line

The return on pharma R&D is not good. There is increasing evidence of zero investment return on R&D in big pharma.

Pharma will lose \$113 billion in revenue over the next five years due to patent expiries.

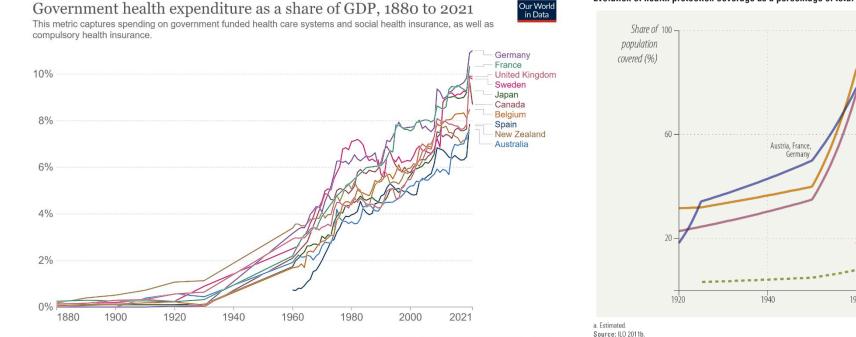
Pharma has little choice but to aggressively acquire biotech companies to replace products that they can't make themselves.

### Reason 5:

### Medical Spend Will Accelerate in the Future

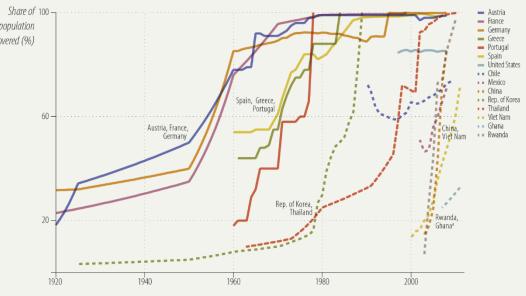
# Health Spending Has Been Rising Quickly Over the Last Century

Spend on healthcare and medicines is continually on the mind of the global consumer – for good reason. The modern period has been defined by rapid and continual expansion of national spending on healthcare through health insurance policies.

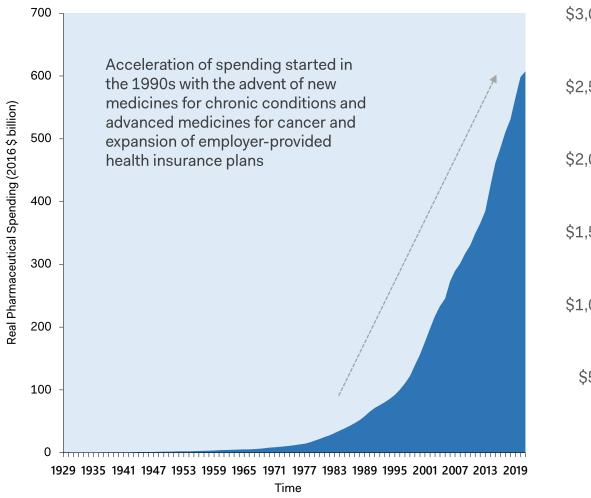


Source: Our World In Data based on Lindert (1994), OECD (1993), OECD Stat OurWorldInData.org/financing-healthcare • CC BY Note: Health spending includes final consumption of health care goods and services (i.e. current health expenditure). This excludes spending on capital investments.

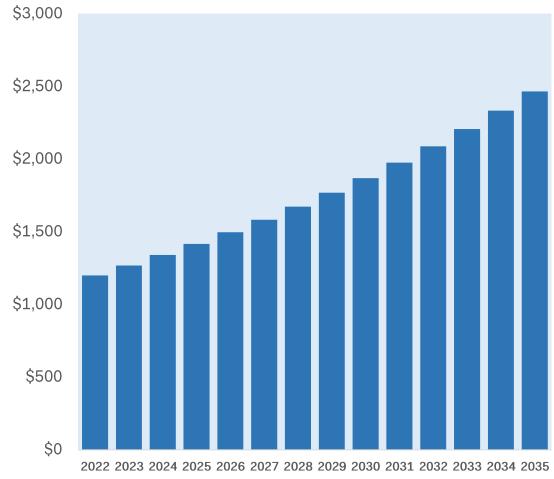
#### Evolution of health protection coverage as a percentage of total population in selected countries



#### Pharma Industry Hypergrowth



#### Total U.S. Pharmaceutical Spending in 2016 Dollars (Billions)

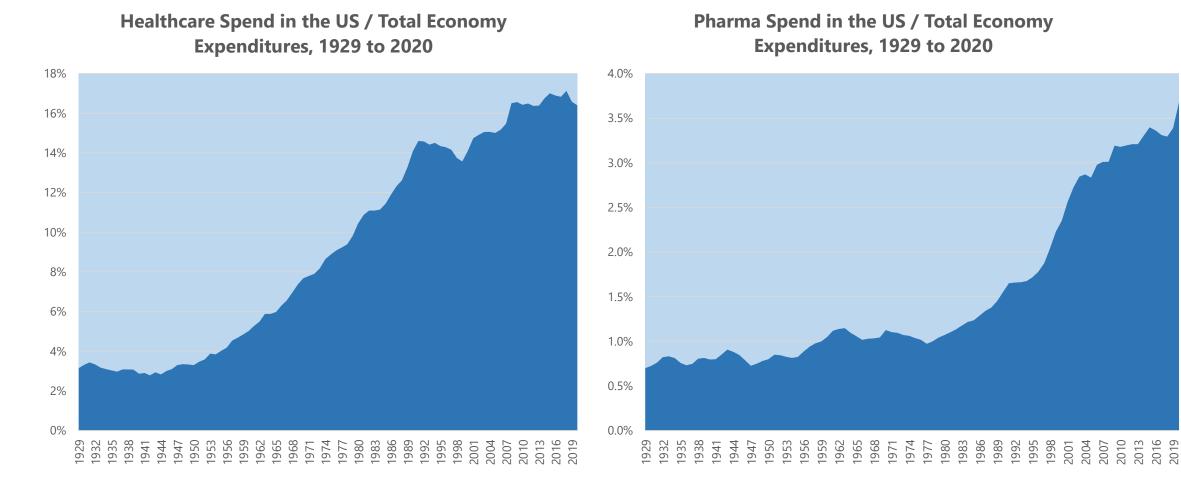


Total Real Global Pharma Spending Forecast, 2022-

2035 (\$ Billions)

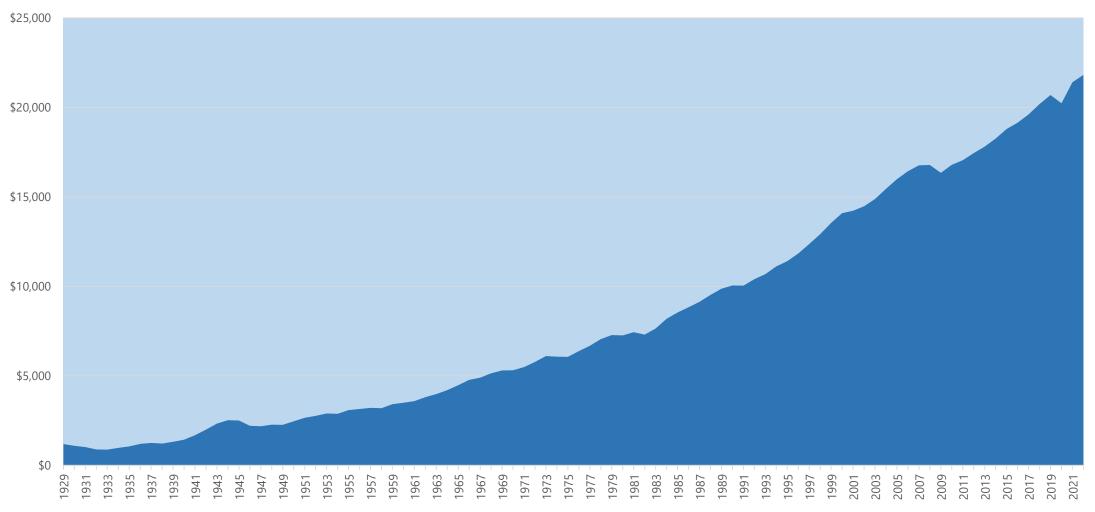
# Medical Spending Rises Disproportionately with National Income

The U.S. Consumer has spent an increasing percentage of wallet on medical care. Once the consumer has covered the basics of food and shelter, he/she directs the marginal dollar to <u>superior goods</u> such as investment in life extension (medical care).



# Real GDP is Up 20-Fold Since 1929

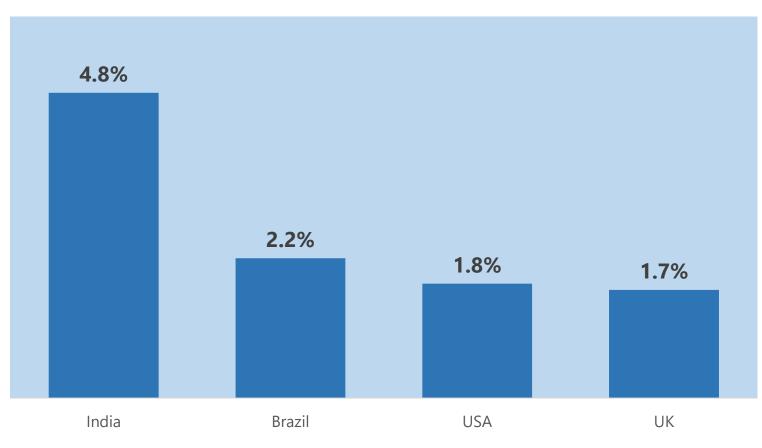
U.S. Real GDP, 1929 to 2022 (Billions, 2017 Dollars)



Source: National Income and Product Accounts of the United States.

# Real GDP Growth Will Continue Indefinitely

Average Projected Real GDP Growth, 2023 to 2050 (PWC Estimate)



PWC forecasts that the U.S. economy will grow at 1.8% in real terms (inflation-adjusted) through 2050.

The global economy will grow faster.

Using the econometric relationship between GDP growth and pharma spend, we should expect to see U.S. pharma spend nearly double by 2050 (only 27 years to go) and global pharma spend more than triple.

# By 2060 Over 90 Million Americans Will be in Medicare

### An Aging Population Will Contribute to Higher Medicare Enrollment

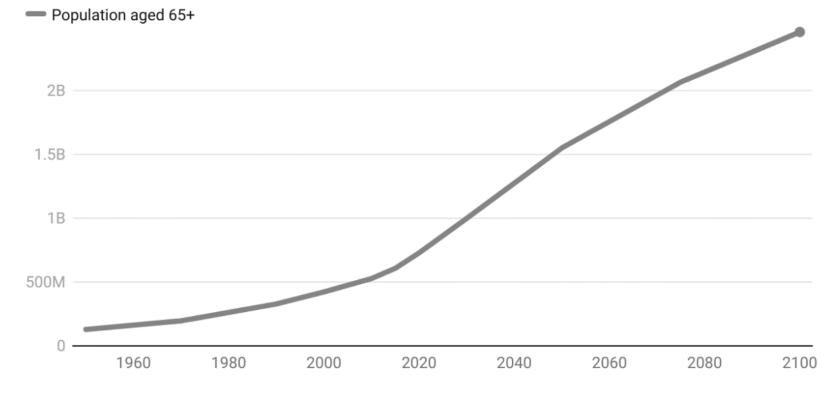
Number of People Enrolled in Medicare, 2020 & 2060



By 2060 There Will be 1.7 Billion People Over 65 in the World

### **More Silver Years**

Size of the global population aged 65 or older from 1950 to 2100 (projected)



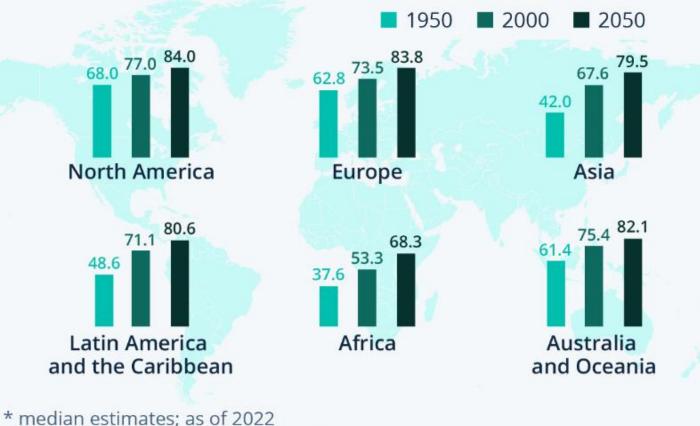
Source: UN Department of Economic and Social Affairs • Created with Datawrapper

### Longer Life Expectancies Imply Increased Medical Spend

Because humans are living longer, they necessarily need to spend more money on medicines – independent of their incomes.

- As persons live longer in industrialized countries their lifetime demand for pharmaceutical and other medical products will rise rapidly.
- In past decades a person may not have survived their first chronic disease whether it be cardiovascular disease or HIV.
- As therapies continue to come online to treat these diseases persons are increasingly likely to face second, third- and fourth-line chronic disease states – particularly diseases of the aged such as Alzheimer's disease and cancer.

Life Expectancy at Birth, 1950 to 2050 by Region

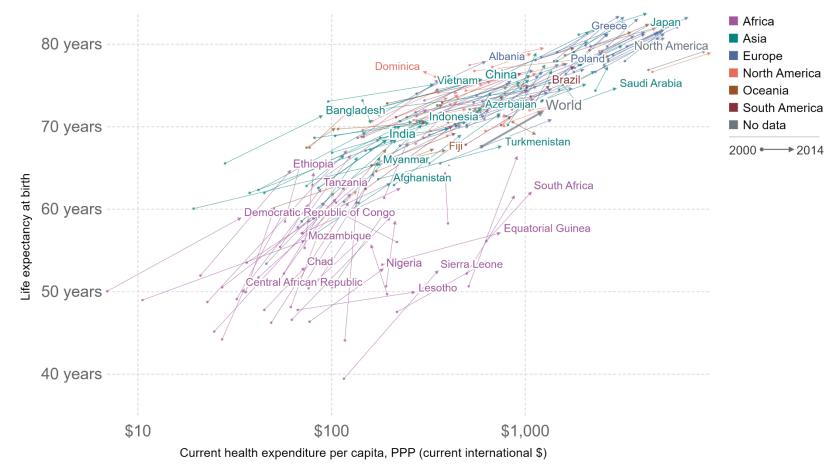


\* median estimates; as of 2022 Source: United Nations Population Division

# Healthcare Spend is Driving Life Expectancy Improvement

### Life expectancy vs. healthcare expenditure, 2000 to 2014

Healthcare expenditure per capita is measured in current international-\$, which adjusts for price differences between countries.



Our World in Data

> There is an interesting feedback loop at play. The more we spend on healthcare as a society, the longer we live.

The longer we live, the more we have to spend on healthcare.

# Public Health and Pharmaceutical Innovation is Playing a Big Role

Buxbaum JD, Chernew ME, Fendrick AM, Cutler DM. Contributions Of Public Health, Pharmaceuticals, And Other Medical Care To US Life Expectancy Changes, 1990-2015. *Health Affairs* 2020 Sep;39(9):1546-1556.

Life expectancy in the US increased 3.3 years between 1990 and 2015, but the drivers of this increase are not well understood. We found that twelve conditions most responsible for changing life expectancy explained 2.9 years of net improvement (85% of the total). Ischemic heart disease was the largest positive contributor to life expectancy, and accidental poisoning or drug overdose was the largest negative contributor. **44% of improved life expectancy was attributable to public health**, **35% was attributable to pharma**, **13% was attributable to other medical care, and (7%) was attributable to other/unknown factors.** 

#### EXHIBIT 3

		Contribu	tion to morta	lity changes					
Categories/ causes of death	Contribution to mortality reduction (%)	Public Pharma- health ceuticals		Other medical Other/ care unexplained		Comments			
CIRCULATORY SYSTEM									
lschemic heart disease Cerebrovascular disease	53	39	52	7	2	Most important pharmaceutical therapie statins, antihypertensives Most important public health improvements: reductions in cholester hypertension, and smoking Most important contributors:			
	10	52	00	0	_	antihypertensives, statins, warfarin			
MALIGNANT NEOPLASMS									
Malignant neoplasms of trachea, bronchus, lung	10	81	5	11	4	Reduced incidence of lung cancer used a proxy for public health factors			
Malignant neoplasm of breast	4	_	60	31	9	Figures reflect 1990–2012 "Other medical care" reflects screening			
Malignant neoplasm of colon, rectum, anus	4	31	27	42	_	Figures reflect experience (1990–200 projection (2000–15) "Other medical care" reflects screenin			
TRAUMA									
Motor vehicle accident	6	90	_	10	_	White infant mortality rate used as prov for medical care Confirmatory findings from second mod			
Homicide	3	91	_	9	_	Aggravated assault rate used as proxy nonmedical contributors to homicide			
NEUROLOGICAL									
Alzheimer disease Dementia, excluding Alzheimer disease	-4 -6	_	_	_	100 100	Possible changes in coding practices Possible changes in coding practices			
OTHER									
Infant mortality HIV/AIDS	8 7	39 —	21 76	20 24	20 —	See exhibit 4 and appendix exhibit A13 Figures reflect physician survey Confirmatory evidence from timing of HAART introduction			
Accidental poisoning or overdose	-9	4	96	_	_	Includes deaths related to opioid crisis			
TOTAL									
All causes	85	44	35	13	-7				

source Authors' analysis of data from the National Vital Statistics System and sources cited in text. Nores Figures reflect 1990-2015 unless otherwise indicated. Figures may differ from totals in text and table because of rounding. HAART is highly active antiretroviral therapy. "See note 7 in text.

### Bottom Line

Medical Products / Pharma spend is going to rise at an increasing rate for the foreseeable future.

Concerns about the IRA, budget deficits etc. miss the larger picture about the effect of rising incomes and longer life spans on medical spend.

There is a key positive feedback loop that many don't see: the more we spend on medicine, the longer we live. The longer we live, the more we have to spend on medicine.

# Reason 6:

# **Biomedical Innovation is Accelerating**

## Massive Change in Medicine Over Last 100 Years

### 1923

- The combined market cap of the pharma sector was less than a half billion dollars.
- Insulin's role in diabetes had just been discovered.
   But insulin was extracted from pig pancreases.
- We did not understand genetics in any meaningful way.
- The leading cause of death was infectious disease. There were no antibiotics.
- Life expectancy at birth was 54 years in the U.S. In China it was 35 years.
- U.S. consumers spent less than 5% of their income on healthcare and less than 1% of their income on pharmaceuticals.

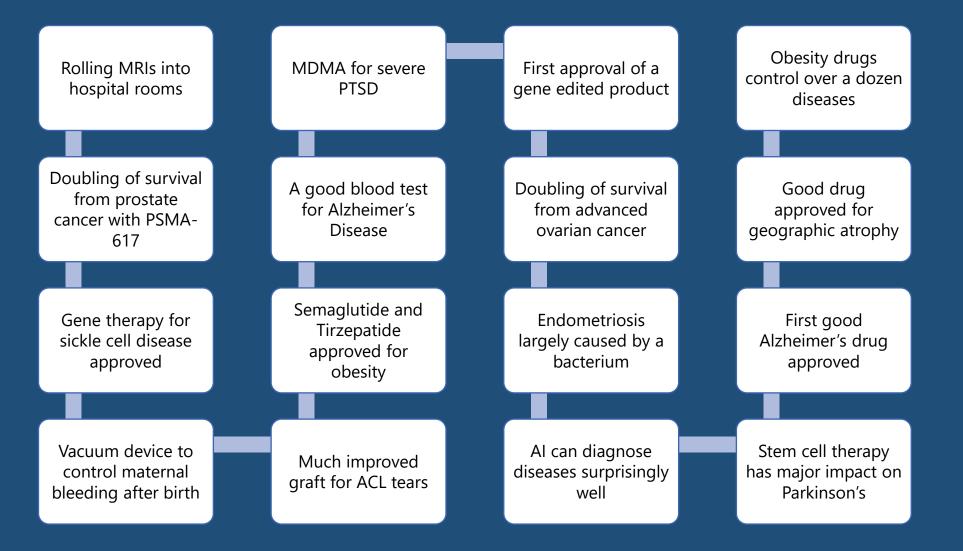
### 2023

- Mortality rates from major diseases including heart disease, cancer and stroke are down dramatically.
- We understand genetics and can manipulate aberrant genes.
- Life expectancy at birth in the U.S. is 79 years. In China it is 77. For a Japanese female over 90.
- Global Pharmaceutical sales are approximately \$1.2 trillion
- The value of the pharma sector is over \$6 trillion (up one thousand-fold from the 1920s).
- U.S. consumers spent nearly a fifth of their income on healthcare and more than 3% of their income on pharmaceutical products.

### We Are Shifting From Two Decades Driven by Tech Into a Multi-Decade Period that Will be Driven by the Life Sciences

- We are seeing a massive acceleration of underlying innovation:
  - Rapidly increasing sophistication of molecular diagnostic tools
  - Deeper understanding of the genetic mechanisms of disease
  - Deeper understanding of how to control diseases at their genetic sources by restoring correctly formed proteins or preventing production of malformed proteins
  - New technologies in gene sequencing, gene therapy, gene editing and RNAi
  - Enormous potential to apply proteomic and metabolomic tools to create precision medicines for patients
  - Deeper understanding of how multiple underlying areas of core physiology (e.g., extracellular matrix deposition, immune function, mitochondrial function, ubiquitination, autophagy, ferroptosis) relate to disease
  - Synthetic biology and ability to impact medicine and broader goods and services
  - Advent of AI and digital technologies with profound implications for design of drugs, execution of trials and delivery of medicine
  - Advent of bioelectronics and ability to control disease with read / write access to the central nervous system
  - Improved access to medicines globally
- The combined effect of these and many other innovations on human life spans in this century will be dramatic.

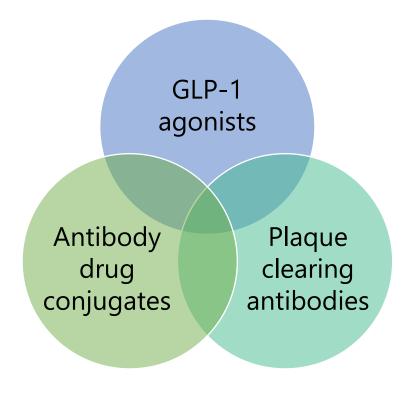
# Countless Medical Advances in the Last 18 Months



The recent pace of medical advances is historic in importance and breathtaking in its speed and breadth.

# Rebecca Sykes of Wellington: Amazing Innovation Today





### 66

The innovations happening in the biopharma industry today are some of

the most exciting I've seen in my career

#### Rebecca Sykes, CFA

Portfolio Manager and Global Industry Analyst

### Debra Netschert of Jennison Sees Massive Innovation

"Advances in DNA sequencing, artificial intelligence, and computational biology in the biotech space have translated into new treatments for chronic diseases such as diabetes and obesity.

There are also early signs that more effective obesity treatments are having a positive impact on cardiovascular disease, which is among the world's deadliest and most costly conditions to treat. For investors, these advancements are creating new opportunities among select pharmaceutical companies that have the depth of resources—including large balance sheets and sizeable manpower—to capitalize on this enormous market for cardiovascular treatments and prevention."



**Debra Netschert** Healthcare Portfolio Manager Jennison Associates

# Linda Thomson of AXA: Genetics Innovation Presents a Major Investment Opportunity

"We expect the first gene-editing drug to be approved this year, taking genetic medicines one step further. Exa-cel, from Vertex and CRISPR Therapeutics, is intended as a one-time treatment that could be life-changing for patients with beta thalassemia or sickle cell disease.

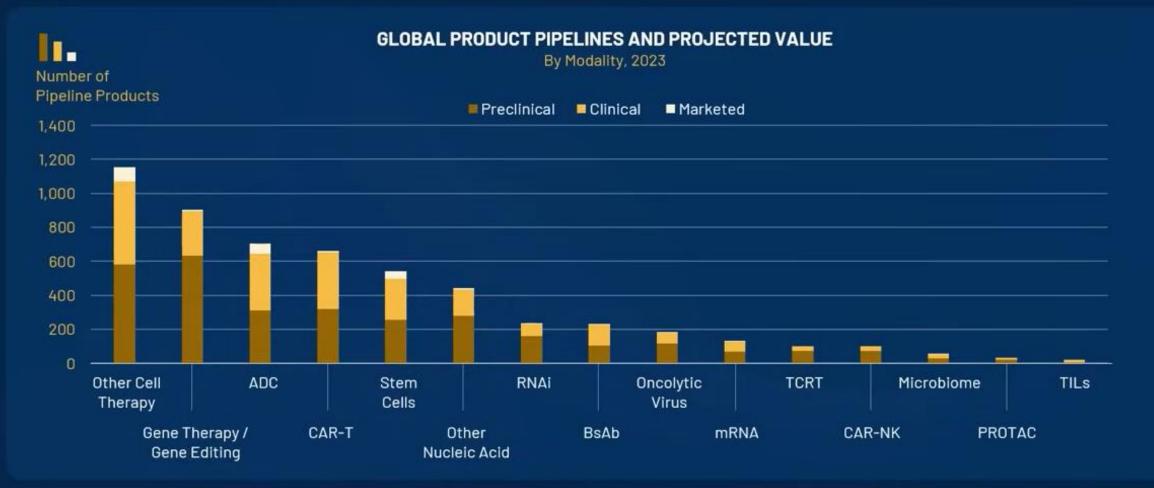
These treatments and drugs give just a brief glimpse at the innovation that is taking place in the biotechnology sector today. Companies across the industry are harnessing genetics to develop their pipelines, building on the advances of the last 70 years to remain at the cutting edge today. We believe that more diseases will find new treatments and perhaps even a cure - and for long-term investors, there is also the scope to potentially reap rewards while funding this vital innovation."



**Linden Thomson** *Portfolio Manager* Axa Framlington

#### June 2023

### **INCREDIBLE NEXT GEN MODALITY DIVERSITY ACROSS THE INDUSTRY**



Source: Boston Consulting Group analysis ("New Drug Modalities 2023" report), including BCG analysis of EvaluatePharma

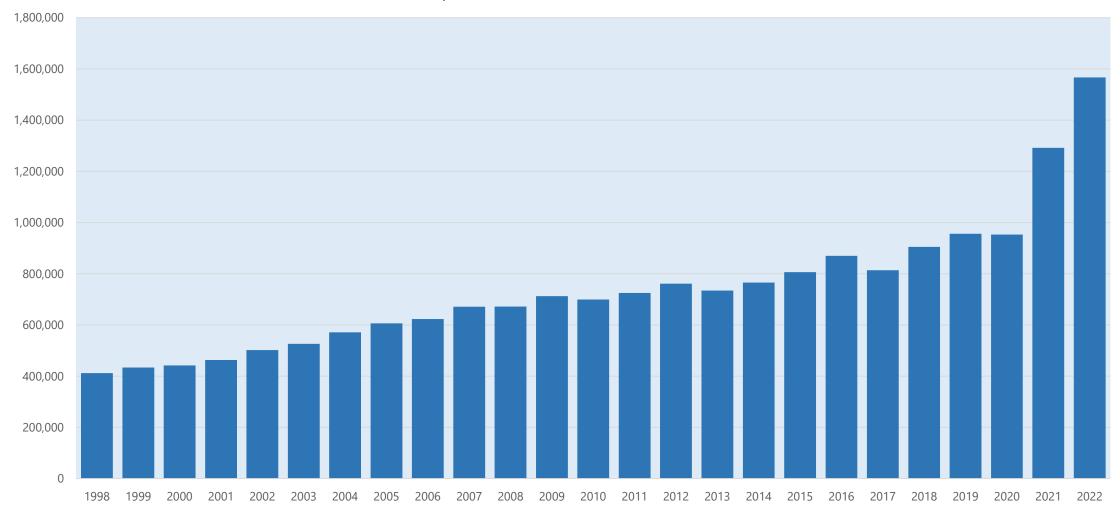


BIOPHARMA INNOVATION

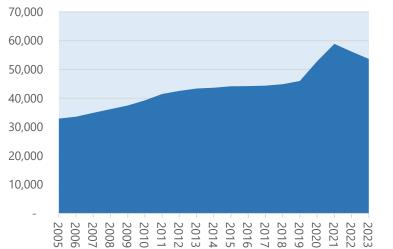


# Biomedical Knowledge is Exploding

New Papers Added to Pubmed, 1998 to 2022



# The Pace of Innovation is Exploding: Publication Counts

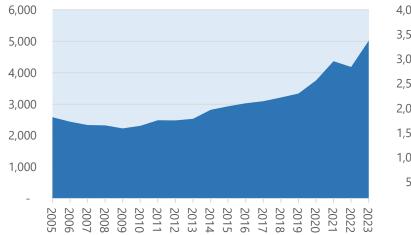


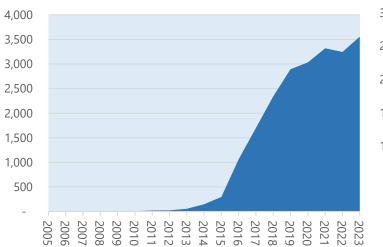
Publication Count in Gene Therapy, 2005-2023

Publication Count in Antibody, 2005 - 2023

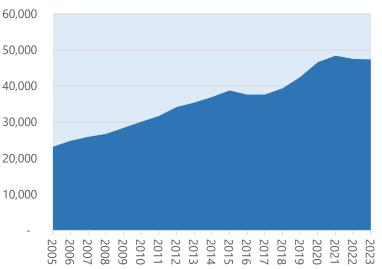
Publication Count in Cell Therapy, 2005-2023

Publication Count in Gene Editing, 2005-2023

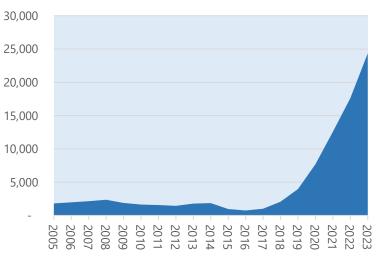




Publication Count in RNA, 2005 - 2023

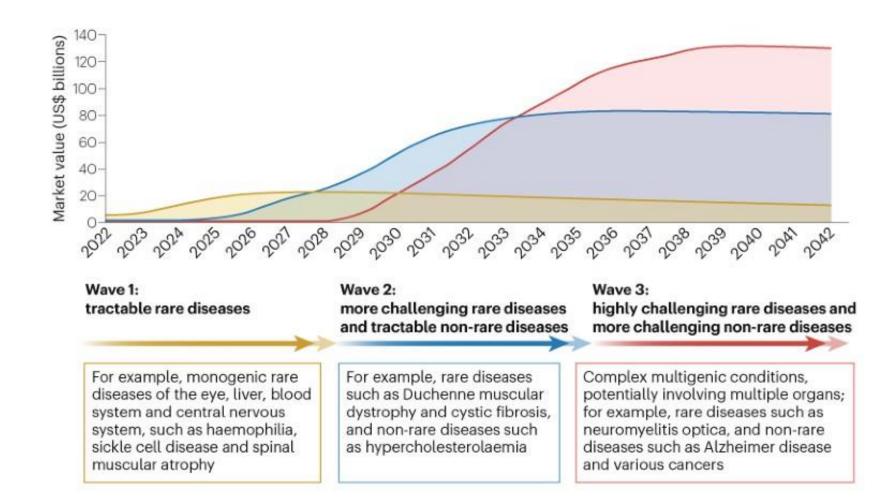


Publication Count in Medical AI, 2005-2023



Source: Pubmed. Note: publication counts for 2023 were annualized as of Nov 1, 2023.

# Huge Opportunity Ahead in Genetic Medicine With More Challenging Multigenic Diseases



"We anticipate that there could be three waves of genomic medicines in the next two decades, driven by therapeutic tractability of different types of diseases and advances with technology platforms."

# Boston Consulting Group 2023

# 1,000-Fold Improvement in Speed / Time to Engineer a New Compound in Fifteen Years

# By Megan Palmer, Andrew Imbrie, Daniel Baer, Anna Puglisi Sunday, *Lawfare*, November 20, 2022

"As observed by synthetic biologist Drew Endy, in 2006 it took the equivalent of 100 postdoctoral researcher years to engineer a three-step pathway in yeast to produce a precursor to a medically relevant compound. Fourteen years later, a roughly 10-fold increase in the sophistication of a comparable strain engineering project took just one year for a single researcher—one one-hundredth of the effort. In other words, we have witnessed 1,000-fold improvements in the ability to engineer biological systems that are capable of generating an enormous diversity of compounds for medicines, fuels, food, materials, and more."

# Giant Opportunity in Cellular Therapy

### Elliott Hershberg, "Medicine's Endgame: Cell Therapy," October 2023

In 2013—only a year after the pair of papers describing the initial clinical CAR-T results—three faculty members from the University of California, San Francisco (UCSF) <u>published an article</u> laying out a vision for cell-based therapeutics as a "third pillar" of modern medicine alongside small molecules and the first wave of biologically derived big molecules. In their estimation, CAR-T was the first of four proposed "killer apps" for cellular medicine.

The four applications were:

- 1. **Engineered immune cells.** CAR-T is one example of the broader vision to engineer immune cells to recognize and cure disease.
- 2. Induced pluripotent stem cell (iPSC) therapy. The 2012 Nobel Prize was awarded to two scientists who discovered that mature human cells can be transformed back into stem cells—the type of cell that can differentiate into any other cell type. This has enormous implications for medicine.
- **3.** Living bacterial cell therapies. Human cells don't need to be the only target for therapeutic engineering. Our bodies contain more bacterial cells than human cells. The microorganisms that live on and in us represent another unique opportunity for genetic reprogramming.
- **4. Multicellular logic systems.** Why stop at engineering one cell type? What if we could develop therapies that leveraged cell-to-cell communication to achieve a precise therapeutic effect?

#### **Cell-Based Therapeutics: The Next Pillar of Medicine**

Biomedicine sits on the cusp of a new revolution: the use of microbial and human cells as versatile therapeutic engines.

MICHAEL A. FISCHBACH , JEFFREY A. BLUESTONE, AND WENDELL A. LIM Authors Info & Affiliations

SCIENCE TRANSLATIONAL MEDICINE · 3 Apr 2013 · Vol 5, Issue 179 · p. 179ps7 · DOI: 10.1126/scitranslmed.3005568

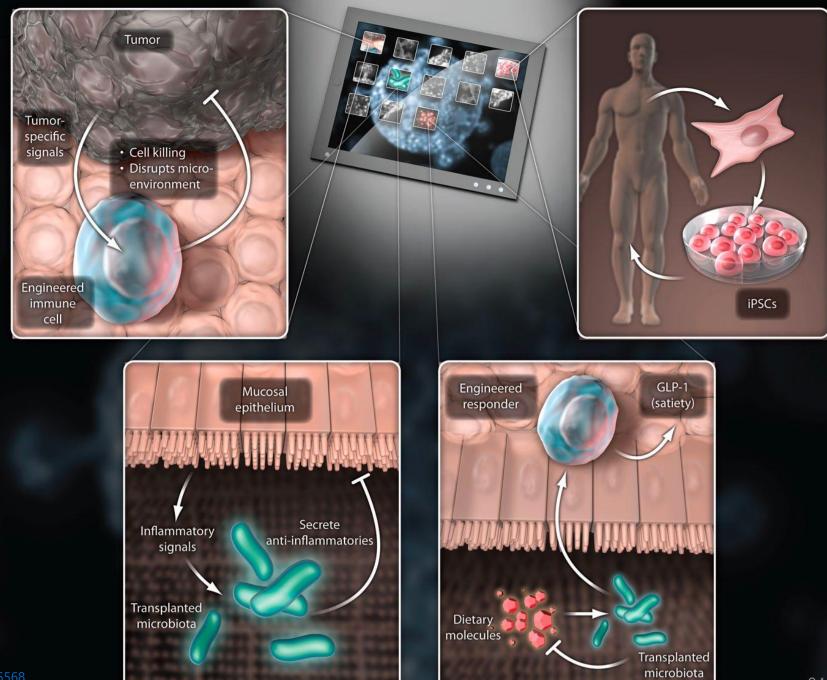
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#### Abstract

Two decades ago, the pharmaceutical industry—long dominated by small-molecule drugs—was revolutionized by the the advent of biologics. Today, biomedicine sits on the cusp of a new revolution: the use of microbial and human cells as versatile therapeutic engines. Here, we discuss the promise of this "third pillar" of therapeutics in the context of current scientific, regulatory, economic, and perceptual challenges. History suggests that the advent of cellular medicines will require the development of a foundational cellular engineering science that provides a systematic framework for safely and predictably altering and regulating cellular behaviors.

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# The Four "Killer Apps" of Cell Therapy



# Cell Engineering: CD19 CAR-T and Carl June

### Elliott Hershberg, "Medicine's Endgame: Cell Therapy," October 2023

Of the first three patients dosed with CART-19, two entered remission. Still, despite their extraordinary results, Dr. June and the Penn researchers reached another impasse. They were on the verge of running out of the philanthropic money used to treat the first patients, and knew they didn't have the resources to statistically prove CAR-T's efficacy. In 2011, June pushed the team to publish a pair of reports in The New England Journal of Medicine and Science Translational Medicine describing their initial findings.

Finally, the world listened. The papers ripped across the biomedical community and the Penn team was approached by a wide range of investors and companies. Rather than starting their own company, June and his team chose the shortest possible path forward for CAR-T to enter the clinic. They decided to license the technology to Novartis, one of the world's largest pharmaceutical companies, in exchange for \$20M of upfront funding to manufacture CAR-T at scale for more studies.

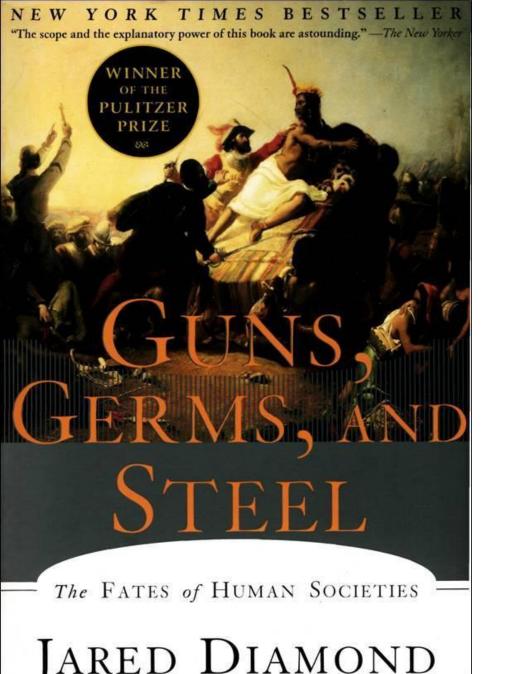
In 2017, Novartis made history by gaining approval to market the CART-19 medicine—now known as Kymriah (tisagenlecleucel)—for a subset of pediatric and young adult ALL patients. In doing so, Kymriah became the first FDA-approved gene therapy. The clinical data leading to its approval was nothing short of remarkable. In a multi-center trial with 63 patients, 83% were in remission within three months.



Emily Whitehead, The First Patient to Receive CAR-T Therapy After Ten Years

# **Reason 7**

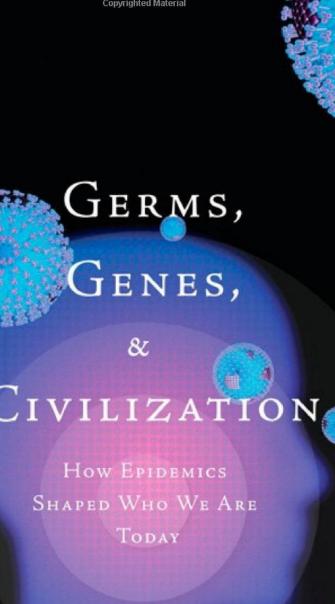
# Biotech Can Change Civilization



The History of Civilization Has Been Shaped by Immunity to Disease

This book's title is a reference to the means by which farm-based societies conquered populations and maintained dominance though sometimes being vastly outnumbered, so that imperialism was enabled by guns, germs, and steel.

Diamond argues geographic, climatic and environmental characteristics which favored early development of stable agricultural societies ultimately led to **immunity to diseases endemic in agricultural animals and the development of powerful, organized states capable of dominating others.** 



ID P. CLARK

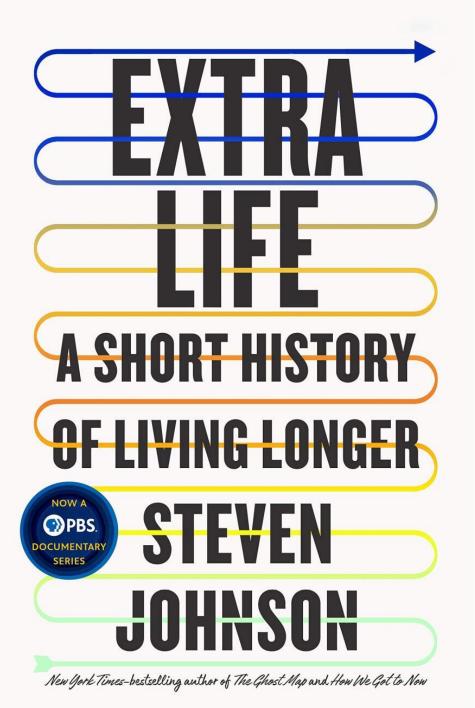
# Infectious Disease Immunity Has Molded Human Destiny

In Germs, Genes and Civilization, David Clark tells the story of the microbe-driven epidemics that have repeatedly molded human destinies.

Epidemics have repeatedly shaped not just our health and genetics, but also our history, culture, and politics. Current gene configurations have been shaped through millennia spent battling against infectious diseases.

### **Epidemics have transformed human history, over and over**

again, from ancient Egypt to Mexico, the Romans to Attila the Hun. The Black Death epidemic ended the Middle Ages, making possible the Renaissance, western democracy, and the scientific revolution.



# Antibiotics and Vaccines Have Changed Modern Society

In 1920, at the end of the last major pandemic, global life expectancy was just over forty years. Today, in many parts of the world, human beings can expect to live more than eighty years. As a species we have doubled our life expectancy in just one century. There are few measures of human progress more astonishing than this increased longevity.

One part of the book focuses on the revolutionary power of vaccines. The speed with which humanity moved from Edward Jenner's linking of milkmaids' apparent immunity to smallpox via cowpox infection to producing effective vaccines for a novel zoonotic virus mere months after it emerged, to say nothing of producing and distributing them on an extraordinary scale, was breathtaking.

Another key part of the book focuses on the development of medical drugs, and thereafter the use of data and the attenuation of social behaviours – is that it embeds the unquestionable success stories in context, particularly antibiotics like penicillin.

The key point is that drug discovery has profoundly shaped human life expectancies and our civilization today.

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GREGORY ZUCKERMAN

IEW YORK TIMES BESTSELLING AUTHOR O The man who solved the market

THE INSIDE STORY OF The Life-or-Death Race For a covid-19 vaccine

# mRNA Vaccines Allowed Our Society to Survive COVID19

Gregory Zuckerman's book *The Shot to Save the World* recounts the decades-long research that underlay the rapid development of not one, but three vaccines against the SARS-CoV-2 virus.

The race to develop a vaccine against SARS-CoV-2 was intense with high stakes. The field was crowded—by late July 2020 there were over 165 vaccine candidates in development and more than 30 in clinical trials using different methodologies. Zuckerman's book tells the story of how two platforms that had not been employed in U.S. licensed vaccines previously were studied, modified, and finalized. Messenger RNA (mRNA) was discovered 60 years ago—it serves as the conduit to interpret genetic material into proteins. By injecting mRNA for virus proteins, the body will read this mRNA and produce virus proteins that the immune system can then recognize, providing future protection against that virus.

This technology ultimately altered the planet – allowing humanity to come out of isolation and begin to work together again.

### "As a Species, We've Arrived at an Unprecedented Moment"

"What a time to be alive. As a species, we've arrived at an unprecedented moment in Evolution. We can now read, write, and edit DNA—the source code of all living organisms.

Advances in DNA sequencing technology have outpaced Moore's Law, becoming the "broadly enabling microscope" of the 21st century. DNA synthesis costs have also exponentially decreased. CRISPR has transformed gene editing from a bespoke, error-prone, and laborious process into a programmable task routinely carried out by graduate students around the world."

**Elliot Hershberg** Stanford University, 2023

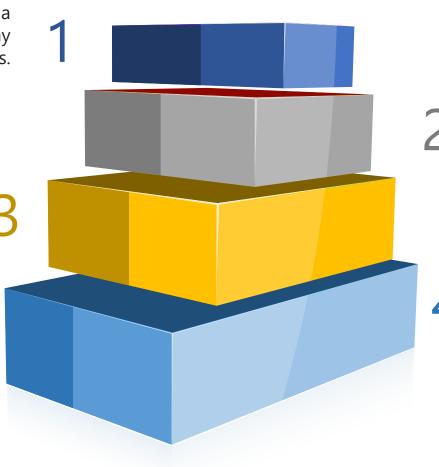


### Medical Innovation Importance Pyramid: **Staging Innovation by Its Impact on Disease and Humanity**

**Incremental**. Will impact a disease in an important way and save some lives.

#### Foundational.

Potential to change the entire field of medicine or dramatically improve treatment of disease related to multiple organ systems. Potential to save 10's of millions of lives.



Occasionally, an innovation comes up that has the potential to change the course of human civilization.

**Important**. Can Innovation that could substantially improve the human condition by altering the treatment of multiple human organ systems or in making a major difference in a top 5 medical condition (cancer, aging, diabetes, Alzheimers, cardiovascular)

#### **Civilization Changing.**

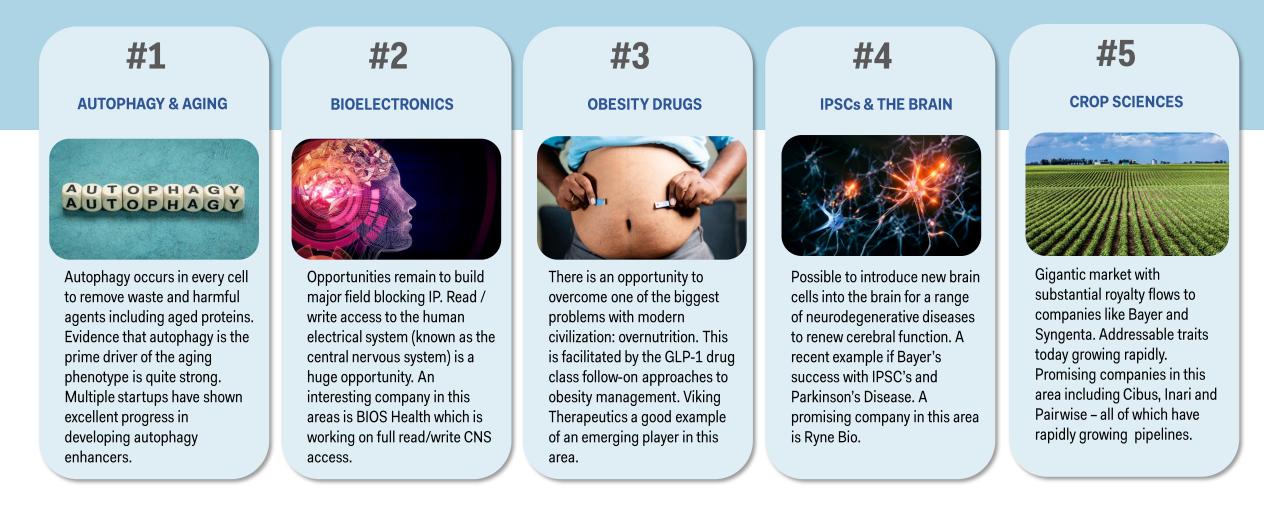
Potential to alter the human experience, the fate of civilizations or to save 100's of millions of lives. Potential to extent average human life expectancy by a year or more. Potential to create giant new industries that employ tens of millions of people.

### Illustrative Areas of Medical Innovation Importance Classified by Position

Incremental	Adenosine drugs Antipurinergics APRIL/BAFF CD47 Cytotoxics Diuretics Fertility Drugs FGF21 FGFR system GNRh antagonists HER2 HIF2a IL-6 IL-23 Levothyroxine Metabolomics NLRP3 NRf2 PSMA RIPK1 RORγt SHP2 STAT3 TROP2 TYK2
Important	ARBs ASOs CD19 CAR-t Ceramide Complement Drugs Degraders ELISA Epigenetics EPO GPCRs HIV Drugs Innate Immunity Ion Channels IVIG JAK KRAS MCR PET Polio Vaccine PPI Statins Steroids TCR drugs TLA1 TNFa TREM2 Thorazine
Foundational	ADCs Amyloid Drugs Anesthesia Antibodies ACE inhibitor Aspirin Ceramides Degraders Epigenetics Epithelial Biology FcRn Drugs Gene Sequencing Gene Therapy IL-4/13 Insulin iPSCs Metformin PD1 mAb Opioids Proteomics RNAi SGLT2 SSRIs
Civilization Changing	Antibiotics / Penicillin Aging & Autophagy Control Bioelectronics Birth Control Pill Discovery of DNA Gene Editing mRNA vaccine Obesity Drugs Precision Medicine and Artificial Intelligence Smallpox Vaccine Synthetic Biology Yamanaka Factors

### Illustrative Promising Areas for Healthcare Investment

The opportunity exists to build civilization-changing companies in these areas.



# Example of a Potential Civilization Changing Technology: Bioelectronics

One key idea advanced by GSK and their joint venture with Verily called Galvani Bioelectronics is to use miniature devices that change nerve electrical signals to address disease:

- Strong prior evidence that this approach works for treating disease
- Technology is at the point where this approach is feasible
- Potential for revolutionary change in medicine can reduce costs of treating disease by orders of magnitude
- Potential to also revolutionize the human experience with direct read and write access to the nervous system
- The associated area of Brain Machine Interface (BMI) also receiving substantial investment

New emerging companies are approaching the problem at a higher level of abstraction. Motivated by the history of computing, new players view the human body as offering direct "read" access to underlying biology and simultaneous ability to "write" to the CNS and impact an action taken by the body. This idea which, a decade ago, might have seen as "SciFi" is now becoming much more of a reality.



Galvani Bioelectronics is a pioneering medical research company dedicated to the development of bioelectronic medicines to treat chronic diseases. Formed through a partnership between two global healthcare companies, GlaxoSmithKline (GSK) and Verily Life Sciences (formerly Google Life Sciences), a subsidiary of Alphabet Inc., Galvani Bioelectronics combines GSK's life science knowledge with Verily's expertise in software and electronics for clinical applications.

Galvani is in human testing of a bioelectronic device for the treatment of rheumatoid arthritis.

# Key Drivers of Bioelectronic Innovation



#### Advances in electrical engineering & miniaturization

"As researchers have learned more about how cells communicate electronically with one another, they are fueling a more sophisticated surge in bioelectronic devices that is delving deeper into more complicated neural networks. Innovations in engineering that are packing chips and other electronic components into tinier and tinier kits to implant in the body, with more power to communicate, charge, stimulate and record, are also expanding the range of diseases that might be treated with a bioelectronic therapy."



#### **Precision Access to the Central Nervous System**

"That's the vision of the future promised by electroceuticals. Nerves in the body that regulate specific organs—really specific cells in those organs—could be controlled with the precision of an orchestra conductor calling on specific instruments to generate just the right harmony. "The nervous system really uses electricity as its language," says Robert Kirsch, chair of biomedical engineering at Case Western Reserve University and executive director of the Cleveland FES Center. "So electrical stimulation can be used theoretically just about anywhere in the nervous system. We need to learn how to speak that language.""



# Jacques Attali: An Early Visionary About Reading the Human Electrical System

Jacques Attali, Age 73, is a French economic and social theorist, writer, political adviser and senior civil servant, who served as a counselor to President François Mitterrand from 1981 to 1991 and was the first head of the European Bank for Reconstruction and Development in 1991-1993. In 2008-2010, he led the government committee on how to ignite the growth of the French economy, under President Nicolas Sarkozy.

In his book *Millennium*, written in 1991 he started to talk about the importance of biosensors and how they could change human life.

The ideas in this book remind one of how Vannevar Bush foresaw the importance of the Web as far back as 1946 in his article "As We May Think".

By 2011 in his book *A Brief History of the Future,* Attali began to talk about biosensors as being central to the human experience in the 21<sup>st</sup> century.

He noted that biosensors will allow humans to monitor their health independently of doctors and governments but that this technology could also be used to control people.

"[By 2050] Electronic bugs, worn subcutaneously, will ceaselessly register heartbeat, blood pressure and cholesterol. Microprocessors connected to various organs will watch their functioning as compared to the norms. Miniature cameras, electronic sensors, biomarkers, nanomotors and nanotubes (microscopic sensors that can be introduced into the pulmonary alveola or the bloodstream) will give everyone the opportunity to measure, permanently or periodically, the parameters of his own body."

Jacques Attali, *A Brief History of the Future*, 2011.

# GALVANI

**GSKs / Verily's Development of a laparoscopic neurostimulator for treating rheumatoid arthritis.** 



Resulting from a major research and development effort over the last five years, the Galvani bioelectronics platform is centered around the world's first fully laparoscopically implanted neurostimulator. It has been tailored for stimulation of nerves to visceral organs and is easily programmed by the treating physician via a wirelessly connected tablet. Patients can also monitor and control their therapy and charge their implant wirelessly.

"The Galvani bioelectronics platform potentially brings a new way to shift the balance from disease to healthy states in a range of immune-mediated and other diseases," said Dr Kristoffer Famm, President of Galvani Bioelectronics.

"The innovative design, rapid development, and rigorous testing of the bioelectronics platform are a combined major achievement by the Verily and Galvani team. We look forward to bringing the wide-ranging potential of splenic nerve stimulation to the clinic as a hopeful new treatment option for people suffering with rheumatoid arthritis," said Stephen Gillett, President and COO of Verily and Galvani Board Director.

In parallel with the UK study, Galvani Bioelectronics has also initiated a larger US-based randomised and double-blinded feasibility study, approved by the U.S. Food and Drug Administration (FDA) under an Investigational Device Exemption (IDE) in the same RA patient population that seek to assess safety as well as effectiveness of the Galvani platform. Patients can currently enroll in Dallas, New York, Austin, Anniston and surrounding areas.

"Immunomodulation using splenic nerve stimulation is a whole new approach to treatment that holds the promise to reduce and potentially resolve the debilitating symptoms of autoimmune diseases, such as RA, from which many patients suffer." said Dr Roy Fleischmann, lead investigator for the US study and Clinical Professor of Medicine at the University of Texas Southwestern Medical Center at Dallas.



iota Biosciences, a wholly-owned subsidiary of Astellas Pharma US, is a medical device company pioneering bioelectronic solutions across a range of medical therapies and diagnostics. Bioelectronic medical implants are the start of an entirely new form of medicine, treating chronic diseases through non-pharmaceutical mechanisms not previously accessible to clinicians.



iota Biosciences, Inc. was acquired by Astellas Pharma US in November 2020. Astellas Pharma US, Inc. is an affiliate of Tokyo-based Astellas Pharma Inc.

Astellas is committed to turning innovative science into medical solutions that bring value and hope to patients and their families.

iota's core proprietary technology stack leverages ultrasonic energy to communicate with and power custom implantable devices, enabling completely new clinical approaches to treating diseases.

iota has made great progress since its acquisition by Astellas.





Kenji Yasukawa, Ph.D., CEO, Astellas

"I believe that iota's technology is a promising core technology that can be applied not only to the current programs we are working on, but to broader types of diseases that have yet to be worked on. I expect that the combination of their capabilities with our strength cultivated through our Rx business will become a strong basis to further drive our Rx+<sup>®</sup> business." Neuralink is an ambitious neurotechnology company that's aiming to upgrade nature's most complex organ — the human brain. Their team of have developed a sleek, innovative, ultra high bandwidth brain-machine interface system that far outshines the status quo.

Co-founded by Elon Musk, Neuralink is building next-generation brain-machine interfaces with scalable neural channel density and real-time data processing unparalleled to anything in the neurotech space.

All connected to their state-of-the-art ASIC, the "N1 Chip," their current system comprises of 3,072 electrodes connected to 96 thin, flexible threads (~4–6  $\mu$ m), far finer than the average human hair.

# NEURALINK

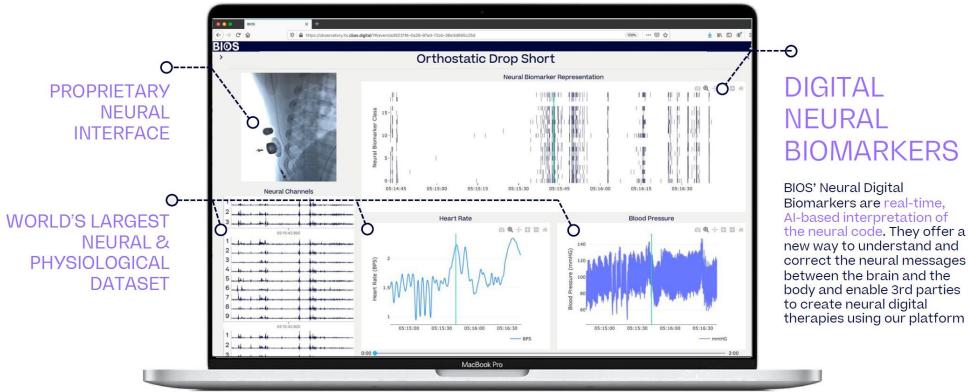
### Elon Musk on Rationale for Neuralink

"Over time I think we will probably see a closer merger of biological intelligence and digital intelligence. It's mostly about the bandwidth, the speed of the connection between your brain and the digital version of yourself, particularly output."

"Some high bandwidth interface to the brain will be something that helps achieve a symbiosis between human and machine intelligence and maybe solves the control problem and the usefulness problem"

# BIOS Health: Read / Write Access to the Human Nervous System

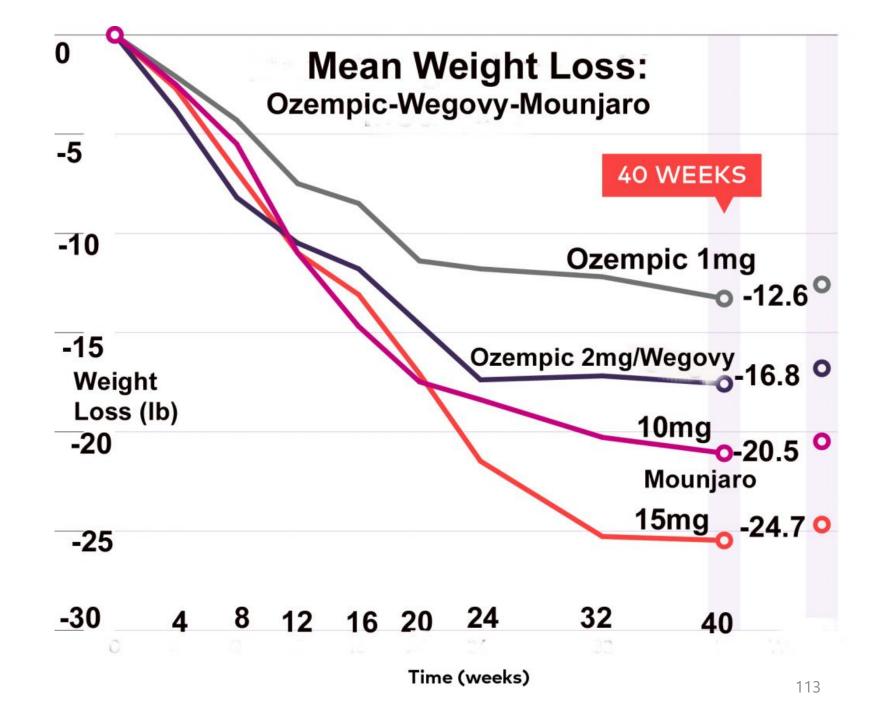
### BIOS CAPTURES, DECODES AND EDITS NEURAL CODE **USING AI**



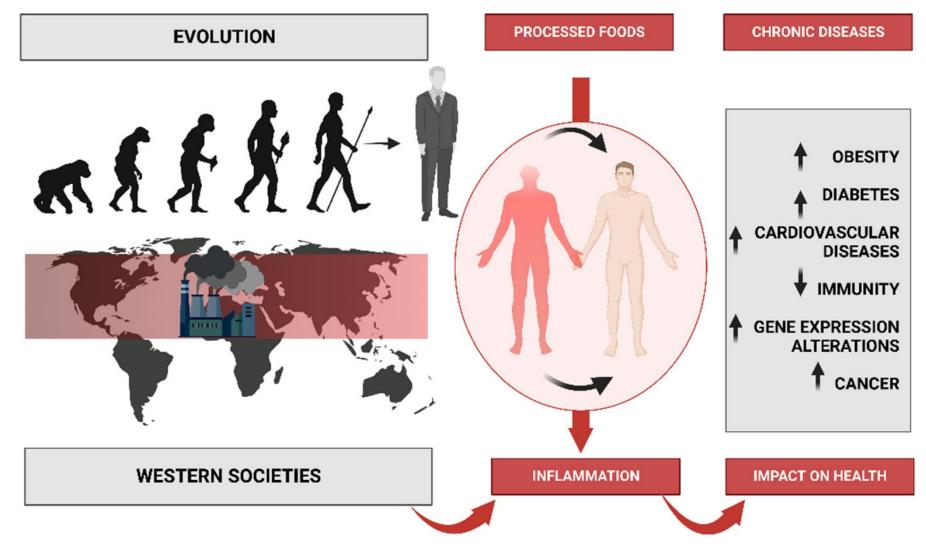


Example of a Potential Civilization Changing Drug: GLP-1 Class Allows Transformational Weight Loss

There is an opportunity to overcome one of the biggest problems with modern civilization: chronic diseases caused by overnutrition.



# We Have Evolved from a World Defined by Infection Disease to One Defined by Chronic Diseases of Overnutrition



### Addressing Obesity is a Civilization Defining Issue

### **OBESITY IS A GLOBAL ISSUE**

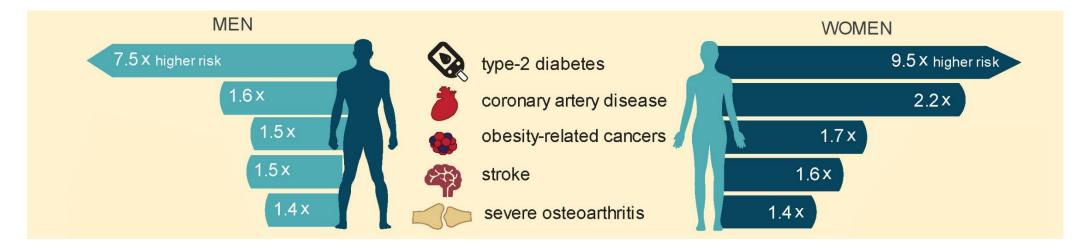


Obesity and Universal Health Coverage





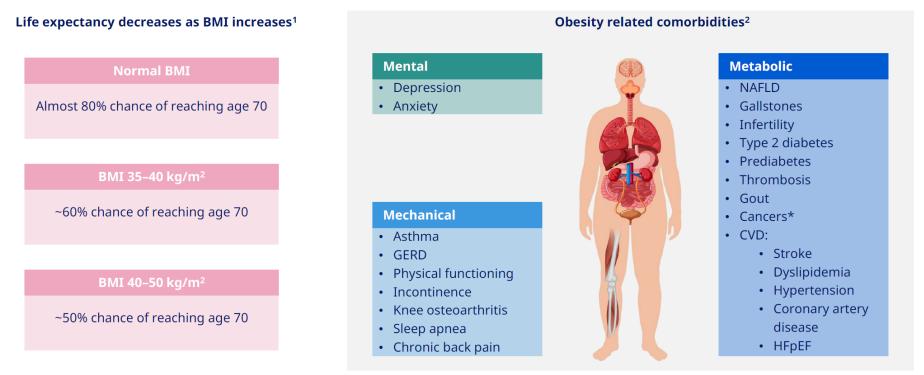
"Approximately 1 in 4 women and 1 in 8 men gain 44 pounds or more between the ages of 18 and 55 years. New research suggests that preventing excessive weight gain during this period may be a promising target for intervention. Weight gain  $\geq$  44 pounds during early to middle adulthood significantly increases chronic disease risk"



Source: https://stop.publichealth.gwu.edu/fast-facts/obesity-related-chronic-disease

### Obesity Has Many Co-Morbidities

### Obesity is associated with multiple comorbidities, which may be improved with weight management



\*Including breast, colorectal, endometrial, oesophageal, kidney, ovarian, pancreatic and prostate

1 Prospective Studies Collaboration, Lancet. 2009;373:1083-96. 2 Adapted from Sharma AM. Obes Rev 2010;11:808-9; Guh DP et al. BMC Public Health 2009;9:88; Luppino FS et al. Arch Gen Psychiatry 2010;67:220-9; Simon GE et al. Arch Gen Psychiatry 2006;63:824-30; Church TS et al. Gastro-enterology 2006;130:2023-30; Li C et al. Prev Med 2010;51:18-23; Hosler AS. Prev Chronic Dis 2009;6:A48. BMI: Body mass index; GERD: gastro-oesophageal reflux disease; HFpEF: heart failure with preserved ejection fraction; NAFLD: non-alcoholic fatty liver disease; CVD: Cardiovascular disease; HFpEF: Heart failure with preserved ejection fraction

# Eric Schmidt Sees Civilization Changing Potential in Synthetic Biology

### Gillian Tett, "Why Eric Schmidt believes bioscience will change the world," *Financial Times*, July 6, 2022 (excerpt)

Eric Schmidt, former CEO of Google, became one of the wealthiest people in the US by specialising in software engineering. Yet, if he was starting out again today, Schmidt says he would not be targeting bits and bytes alone. The 67-year-old thinks the next big thing is the "bioeconomy", not the internet. This catch-all label, Schmidt explained to me at the Aspen Ideas forum last month, describes "the use of biological processes to make use of things that we consume and manufacture... advances in essentially molecular biology... plus advances in AI have allowed us to do new techniques and grow new things."

Helpfully, he listed a few innovations this economy might include: new plastics that naturally degrade without polluting water, "biologically neutral" cement that does not hurt the environment, soil microbes that reduce fertiliser use, soy-based roof-coating that reduces urban heat and, my favourite, compostable dining ware such as edible forks. Put another way, the bioeconomy is based on stuff that is grown using synthetic biology.

### "Molecules are becoming the new microchip," echoed Walter Isaacson, the prolific biographer and former Time Magazine editor, also at the Aspen forum. "Molecules are able to be reprogrammed the way we reprogrammed microchips."

The small difference, Isaacson said, is that in synthetic biology "the code is not digital, or binary with zeros and ones, but it has four letters". For Isaacson the key is that synthetic biology, like computing, is rooted in an "information revolution", which for the bioeconomy started around the millennium when the human genome was sequenced.

Despite the obstacles, both Schmidt and Isaacson insist that the long-delayed revolution is ready to accelerate. That is partly down to advances in science that have been helped by the application of AI. "The technologies didn't work 10 years ago, but they do now," says Schmidt. For Isaacson, "This stuff has been kicked up a notch because scientists have now realised that they cannot only read the code [of DNA] but edit it too."

### BlueRock Therapeutics / Bayer

BlueRock's Phase I study with bemdaneprocel in patients with Parkinson's disease meets primary endpoint

**Berlin, Germany, Cambridge, MA USA, August 28, 2023** – Bayer AG and BlueRock Therapeutics LP, a clinical stage cell therapy company and wholly owned independently operated subsidiary of Bayer AG, announced today details of the positive data from the Phase I clinical trial for bemdaneprocel (BRT-DA01), a stem cell derived investigational therapy for treating Parkinson's disease. The data were presented at the International Congress of Parkinson's Disease and Movement Disorders<sup>®</sup> in Copenhagen, Denmark.

The study met the primary objective of demonstrating safety and tolerability in all 12 participants in the study's low and high dose cohorts, with no serious adverse events (SAEs) reported related to bemdaneprocel through one year. There were two SAEs reported that were unrelated to bemdaneprocel, one seizure attributed to the surgical procedure and one COVID case. Both resolved without sequelae. In addition, 18F-DOPA PET imaging scans demonstrated evidence of cell survival and engraftment in both low and high dose cohorts. 18F-DOPA PET imaging is a neuroradiological technique used to visualize and assess dopaminergic activity in Parkinson's disease.

Secondary exploratory clinical endpoints improved in both cohorts, with participants in the high dose cohort showing greater improvement, as assessed by the MDS-Unified Parkinson's Disease Rating Scale Part III (MDS-UPDRS Part III) and the Hauser Diary, which are tools used to assess Parkinson's disease severity in motor symptoms.



Orange-stained areas show dopamine producing neurons increased after IPSC therapy.



"The data from this Phase I open label study are extremely encouraging. While this is a small open-label study, meeting the study's primary objective for safety and tolerability along with initial improvements seen in clinical outcomes represents a great step forward. The hope now is that these trends continue and translate into meaningful benefit for people with Parkinson's disease in controlled clinical trials."

### **Claire Henchcliffe**

Chair, Department of Neurology at the University of California, Irvine



An improvement in MDS-UPDRS Part III OFF time and patient-reported ON and OFF time was

Part III score (OFF); B) Patient-reported Good ON time without troublesome dyskinesia;

Figure 4. Change from baseline in Cohort A (Blue) and Cohort B (Teal) in A) MDS-UPDRS

MDS-UPDRS Part III score (OFF)

Patient-reported Good ON time without troublesome du

.

Line represents the median change for the cohort, circle represents the mean, the box represents the lower and upper quartiles and the whiskers represent the extremes. Patient-reported ON time with troublesome dyskinesis

Cohort A (N=5)

1.0(-26.0, 13.0)

-0.72 (-0.4.1.0)

-1.62 (-1.7, -0.4)

0.72 (-0.7, 2.0)

Visit (week

Cohort B (N=7)

-13.0 (-20.0, -4.0)

2.16 (-0.4, 2.2)

0.0 (-0.3, 0.0)

-1.91 (-2.2, 0.4)

26 39 52

emonstrated no clinically meaningful change through Week 52 (Table 4).

hange in MDS UPDRS Part III Score at Year 1 from baseline, median (Q1, Q3)

Table 4. Change in clinical outcomes at Year 1 from baseline

rted change in clinical scores at Year

ood ON time without troublesome dyskinesi

Visit (week)

Improvements in median clinical scores were greater in Cohort B compared with Cohort A

Henchcliffe C<sup>1</sup>, Sarva H<sup>2</sup>, Lozano A<sup>3-5</sup>, Fasano A<sup>4</sup>, Kalia S<sup>4</sup>, Yu K<sup>6</sup>, Brennan C<sup>6</sup>, Stemple W<sup>7</sup>, Abid N<sup>7</sup>, Yountz M<sup>7</sup>, Enayetallah A<sup>7</sup>, Lampron A<sup>7</sup> and Tabar V<sup>6</sup>

1. Department of Neurology University of California, CA, Irvine, United States of America. 2. Department of Neurology, Weill Cornell Medicine, New York, NY, United States of America. 3. Edmond J. Safra Program in Parkinson's Disease, Morton and Gloria Shulman Movement Disorders Clinic, Toronto Western Hospital, UHN, Toronto, Ontario, Canada. 4. Division of Neurology, University of Toronto, Toronto, Ontario, Canada. 5. Krembil Brain Institute, Toronto, Ontario, Canada. 6. Department of Neurosurgery and Center for Stem Cell Biology, Memorial Sloan Kettering Cancer Center, New York, NY, United States of America. 7. BlueRock Therapeutics LP, Cambridge, MA, United States of America.

#### Introduction

Current treatments for Parkinson's disease (PD) do not address dopaminergic neuron loss, an underlying cause of disease. In addition, current treatments do not impact disease progression and lose effectiveness over time.1,2

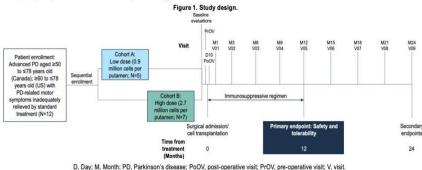
Bemdaneprocel (BRT-DA01) is an investigational therapy comprised of dopaminergic neurons derived from pluripotent stem cells.<sup>3</sup> Studies in Parkinsonian mouse models showed no significant safety findings in biodistribution, toxicology or tumorigenicity studies. Preclinical efficacy was demonstrated in rats.<sup>2</sup>

We report the Year 1 outcomes of a multi-center, multi-site, open-label, non-randomized, Phase 1 (NCT04802733) study to assess the safety and tolerability, as well as exploratory efficacy measures, of bemdaneprocel in participants with PD.

#### Participants, Methods & Analysis

#### Study population:

 Participants were sequentially recruited into this Phase 1 study. The first five participants were enrolled into the low-dose group (0.9 million cells per putamen) and subsequent participants were enrolled into the high-dose group (2.7 million cells per putamen) (Figure 1) All participants were enrolled from 03 May 2021 through 30 March 2022



#### Methods:

- · Cells were administered in a single session of stereotactically guided surgical injection into the posterior putamen bilaterally through a single burr hole on each side. Cells were delivered using three passes of the cannula on each side and 3 cell deposits per pass, for a total of 9 cell deposits per hemisphere (Figure 2)
- An immunosuppressive regimen was initiated intraoperatively and continued post-operatively for 1 year
  - Participants were initiated on an immunosuppressive regimen of basiliximab 20 mg intravenously intraoperatively and post-operative on Day 4; methylprednisolone 500 mg intravenously prior to surgery, then tapered to oral prednisone and continued at 5 mg daily for 1 year; tacrolimus taken orally beginning on the day after surgery (Day 1) and then adjusted to a target trough blood level of 4-7 ng/mL for a period of 1 year

#### Analysis:

- The primary objective of the study was to assess safety and tolerability, with a primary endpoint measuring the incidence of serious adverse events (SAEs) at 1-year post-transplant
  - Safety was defined as 2 or fewer patients of Cohort A or Cohort B (a) developing 2 or more SAEs related to surgery, presence of transplanted cells or immunosuppression; (b) developing a tumor or abnormal tissue overgrowth related to presence of transplanted cells; (c) developing an intracerebral hemorrhage that is deemed to be life-threatening; (d) experiencing 1 or zero deaths

Figure 2. Surgical approach.

Depiction of the surgical tracks of administration.

- In addition, the following secondary and exploratory endpoints were also assessed at Year 1
  - Changes from baseline in striatal fluorodopa (18F-DOPA) uptake using positron emission tomography (PET)
  - Changes from baseline in the International Parkinson and Movement Disorder Society (MDS)-Unified Parkinson's Disease Rating Scale (UPDRS) motor sub-score in the OFF medication state
  - Changes from baseline in the number of hours in the ON state without troublesome dyskinesia, OFF state and ON state with troublesome dyskinesia
  - Feasibility, as defined by intra-operative delivery of at least 50% of the intended number of deposits per brain in >50% of subjects Incidence and type of adverse events (AEs)

#### Patient disposition

- · Patient baseline characteristics were comparable across both cohorts (Table 1) All participants received their planned dosage
- All participants (N=12) were included in the safety and evaluable populations Table 1 Baseline characteristics

	Cohort A (N=5)	Cohort B (N=7)	Total (N=12)
Age, years			
Mean (SD)	66.8 (6.80)	66.7 (4.79)	66.8 (5.41)
Median (Q1, Q3)	67.0 (65.0, 67.0)	68.0 (64.0, 70.0)	67.0 (64.5, 70.0)
Sex, n (%)			
Male	4 (80.0)	5 (71.4)	9 (75.0)
Female*	1 (20.0)	2 (28.6)	3 (25.0)
Race, n (%)			
American Indian or Alaska Native	0	0	0
Asian	0	1 (14.3)	1 (8.3)
Black or African American	0	0	0
Native Hawalian or other Pacific Islander	0	0	0
White <sup>†</sup>	3 (60.0)	5 (71.4)	8 (66.7)
Other	1 (20.0)	1 (14.3)	2 (16.7)
Multiple	1 (20.0)	0	1 (8.3)
Time since PD diagnosis, years			
Mean (SD)	11.0 (3.68)	7.8 (2.19)	9.1 (3.21)
Median (Q1, Q3)	12.7 (8.9, 13.7)	8.2 (5.3, 10.2)	9.0 (5.9, 11.5)
Hoehn and Yahr Stage (OFF state), n (%)			
0&1	0	0	0
2	1 (20.0)	0	1 (8.3)
3	4 (80.0)	7 (100)	11 (91.7)
48.5	0	0	0
Hoehn and Yahr Stage (ON state), n (%)			
0&1	0	0	0
2	5 (100)	7 (100)	12 (100)
3,485	0	0	0

Safety

There were no reports of an AE or SAE related to bemdaneprocel (Table 2) There was 1 SAE of seizure that was transient attributed to the surgical procedure

reported in Cohort B

#### Table 2. Summary of treatment-emergent serious adverse events (TESAEs) at Year 1.

	Cohort A (N=5)		Cohort B (N=7)			
Subjects reporting, n (%) [Total number of events]	0 events	1 event	≥2 events	0 events	1 event	≥2 event
TESAE	4 (80.0)	1 (20.0) [1]*	0	6 (85.7)	1 (14.3) [1]	0
Related to surgery	5 (100)	0	0	6 (85.7)	1 (14.3) [1]	0
Related to cell product	5 (100)	0	0	7 (100)	0	0
Related to immunosuppressive drugs	5 (100)	0	0	7 (100)	0	0
Tumor or abnormal tissue overgrowth related to presence of transplanted cells	5 (100)	0	0	7 (100)	0	0
Intracerebral hemorrhage that is deemed to be life-threatening	5 (100)	0	0	7 (100)	0	0
Deaths		0			0	

and tolerating the 1-year immunosuppression regimen

Bemdaneprocel was generally safe and well tolerated in these 12 participants at 1-year post-transplantation

The stereotactic surgical delivery and therapeutic regimen was feasible, with all participants receiving the planned dose of bemdaneprocel

Evidence of bemdaneprocel survival and engraftment was demonstrated in the posterior putamen by 18F-DOPA PET imaging

#### Results

- 11/12 participants reported TEAEs (66 events in total: Table 3)
- · Most TEAEs were mild or moderate in severity
- One severe TEAE was reported There were no discontinuations or deaths in the study
- . There were no graft-induced dyskinesias seen in either cohort
- many of treatment-emergent adverse events (TEAFs) Table 3 St

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	Cohort A (N=5)	Cohort B (N=7)	Total (N=12)
Subjects reporting, n (%) [Total numbe	er of events]		
TEAE	5 (100) [39]	6 (85.7) [27]	11 (91.7) [66]
TEAE by maximum Common Terminol events]	ogy Criteria for Adverse Eve	ints (CTCAE) Grade, n (%)	[Total number of
Grade 1: Mild	1 (20.0) [28]	3 (42.9) [24]	4 (33.3) [52]
Grade 2: Moderate	3 (60.0) [10]	3 (42.9) [3]	6 (50.0) [13]
Grade 3: Severe	1 (20.0) [1]	0	1 (8.3) [1]
Grade 4: Life-threatening	0	0	0
Our de C. Durath and stand to AF		0	

#### 18F-DOPA uptake

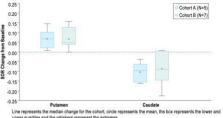
B)

- At a group level there was an increase in <sup>18</sup>F-DOPA uptake in the posterior putamen (transplant site), which did not associate with the degree of baseline <sup>18</sup>F-DOPA uptake (Figure 3)
- A decrease in <sup>18</sup>F-DOPA was observed in the caudate nucleus (distant from the site of transplantation)

#### Figure 3. Group level analysis of <sup>18</sup>F-DOPA PET uptake in the striatum.

A) Voxel based analysis of the 18F-DOPA PET data was conducted. Voxel clusters with low p-value (P<0.05) group level changes between baseline and 1 year SOR signal within the caudate and putamen are displayed (voxels with increase in orange, voxels with decrease in blue). B) Change in striatal-to-occipital ratio (SOR) from baseline limited to voxel clusters with low p-values (P<0.05). Changes within these clusters for the caudate and putamen are combined for each subject using volume weighted means





upper quartiles and the whiskers represent the extreme

#### Conclusions

Analysis of clinical scores may suggest improvement in MDS-UPDRS Part III (OFF state), a decrease in OFF time, and an increase in Good ON time without troublesome dyskinesia

OFF time

ON time with troub

\*Reported via Hauser Dian

Clinical outcomes

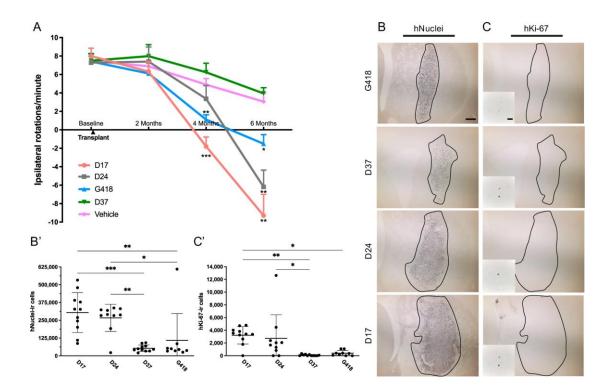
seen (Figure 4; Table 4)

C) Patient-reported OFF time

- No graft-induced dyskinesias occurred through 1 year
- Although efficacy trends were present across both cohorts, Cohort B showed a greater magnitude of changes. However, it is important to note that these efficacy analyses are limited by the small sample size and the uncontrolled trial design, and interpretation must there fore be cautious

# Example of an Emerging Player in IPSC's: Ryne Bio:

- Replacing neurons that are lost during a degenerative neurologic disorder is a new approach to advancing disease-modifying treatments.
- Ryne has developed an iPSC dopamine progenitor (RNDP-001) that displays superior survival, innervation, and behavioral rescue in a Parkinson's Disease model.
- As shown in the paper at right, Ryne is able to achieve durable engraftment of dopamine generating iPSC's in Parkinson's models.
- RNDP-001 has successfully completed FDAmandated preclinical safety studies and is now moving into clinical manufacture for IND and Ph1 clinical trials.



Time-based analysis of A d-amphetamine-induced rotations measured pre-operatively and at 2, 4, and 6 months postengraftment. At 4 months post-transplantation, P < 0.0005 for D17 and P < 0.005 for G418; at 6 months posttransplantation, P < 0.0005 for D17 and D24 and P < 0.05 for G418. Data were analyzed by mixed ANOVA with Tukey's adjustment; error bars are SEM. Comparisons were made to vehicle group. Representative graft sections stained for B hNuclei and C hKi-67 with graft borders indicated by black outline. Quantification by unbiased stereology of B' hNuclei-ir (P < 0.0001 D17 vs. D37/G418; P < 0.0005 and P < 0.005 for D24 vs. D37/G418, respectively) and C' hKi-67-ir cells (P < 0.05 for D17 vs. D37; P < 0.01 for D17 vs. G418; P < 0.05 for D24 vs. D37). Scale bar = 500  $\mu$ M in B; 50  $\mu$ M in C (inset). hNuclei estimates were analyzed by one-way ANOVA with Tukey's adjustment; error bars represent SD. hKi-67 estimates were analyzed by Kruskal–Wallis test and Dwass–Steele–Critchlow-Fligner post hoc. \*p < 0.05 \*\*p < 0.001 \*\*\*p < 0.0001.

## Example of a Potential Civilization Changing Technology: Autophagy Enhancers

### Ren J, Zhang Y. Targeting Autophagy in Aging and Aging-Related Cardiovascular Diseases. Trends Pharmacol Sci. 2018 Dec;39(12):1064-1076

"Aging, an irreversible biological process, serves as an independent risk factor for chronic disease including cancer, pulmonary, neurodegenerative and cardiovascular diseases. In particular, high morbidity and mortality has been associated with cardiovascular aging although effective clinical therapeutic remedy is suboptimal for the ever-rising aging population.

Recent evidence suggests a unique role for aberrant aggregate clearance and protein quality control machinery - the process of autophagy in shortened lifespan, compromised healthspan, onset and development of aging-associated cardiovascular diseases.

Autophagy degrades and removes long-lived or damaged cellular organelles and proteins, the functions of which decline with advanced aging. Induction of autophagy ... delays aging, prolongs lifespan and improves cardiovascular function in aging. Given the ever-rising human lifespan and aging population as well as the prevalence of cardiovascular disease provoked with increased age, it is pertinent to understand the contribution and underlying mechanisms for autophagy and organelle-selective autophagy (e.g., mitophagy) in the regulation of lifespan, healthspan and cardiovascular aging. Here we will dissect the mechanism of action for autophagy failure in aging and discuss the potential rationale of targeting autophagy."

We have reviewed dozens of papers on aging biology and stories regarding modifiable risk factors.

There are many interesting approaches being taken including Yamanaka factors.

The evidence suggesting that autophagy enhancement would make a major difference emerged as particularly strong from our review.

# Huntington's Disease a Good Model Disease of Role of Autophagy in Aging Process

#### Genetic Engineering and Biotechnology News, October 31, 2022 (excerpt)

Huntington's disease (HD) is a neurodegenerative disorder in which the clinical symptoms appear in adulthood. Despite the lack of symptoms earlier in life, the mechanism by which aging drives the onset of neurodegeneration in patients with HD remains unclear. Now, scientists have studied striatal medium spiny neurons (MSNs) directly reprogrammed from fibroblasts of patients with HD. Huntington's disease specifically destroys the medium spiny neurons, the loss of which causes involuntary muscle movements, impaired mental health, and cognitive decline. Patients typically live about 20 years after signs of the disease first appear.

By modeling the age-dependent onset of pathology, the researchers found that, as patients age, the disease gradually impairs autophagy—a process responsible for eliminating waste from cells. This housekeeping is significant in Huntington's because a buildup of waste leads to cell death. They went on to show that enhancing the autophagy pathway in such neurons that were created from skin cells of Huntington's patients protects those cells from dying.

This work appears in *Nature Neuroscience* in the paper, "Age-related Huntington's disease progression modeled in directly reprogrammed patient-derived striatal neurons highlights impaired autophagy."

"Our study reveals how aging triggers a loss of the crucial process of autophagy—and hints at how we might try to restore this important function, with the aim of delaying or even preventing Huntington's disease," said Andrew Yoo, PhD, a professor of developmental biology at the Washington University School of Medicine in St. Louis. For this study, the researchers reprogrammed patients' skin cells into medium spiny neurons. The study also uncovered what may be a tantalizing clue for understanding cognitive decline in normal aging. When comparing the symptomatic neurons to pre-symptomatic neurons and to healthy neurons from both young and older adults, the researchers found that the neurons of healthy older adults produced slightly elevated levels of the harmful microRNA, but in far smaller amounts than the neurons of symptomatic Huntington's disease patients. The study suggests that even in normal, healthy aging, medium spiny neurons gradually produce low levels of this microRNA, which may interfere with autophagy's healthy cellular housekeeping.

"By modeling different stages of the disease across the life span, we can identify how aging plays a role in disease onset," Yoo said. "With that information, we can begin to look for ways to delay that onset. Our study also suggests that the triggering molecule for the onset of Huntington's disease may play some role in age-associated decline in neuronal function generally. Understanding the component of aging that sets off neurodegeneration may help in developing new strategies for treatment and prevention of Huntington's disease and other neurodegenerative conditions that develop at older ages."

Yoo and his team are also working with other collaborators using their cellular reprogramming technique to investigate forms of Alzheimer's disease, tauopathy, and other neurodegenerative conditions.

# G2 Analogs Effective in Enhancing Autophagy in Huntington's Disease Model

Oh YM, Lee SW, Kim WK, Chen S, Church VA, Cates K, Li T, Zhang B, Dolle RE, Dahiya S, Pak SC, Silverman GA, Perlmutter DH, Yoo AS. Age-related Huntington's disease progression modeled in directly reprogrammed patientderived striatal neurons highlights impaired autophagy. Nat Neurosci. 2022 Nov;25(11):1420-1433.

"In this study, we leveraged the conversion system to investigate how aging in Huntington's Disease may contribute to MSN degeneration by focusing on the finding that the degree of neuronal death in patient-derived MSNs corresponds to the stage of HD progression. MSNs converted from fibroblasts collected after the onset of clinical symptoms (HD-MSNs) display significantly higher levels of cell death than MSNs reprogrammed from patient fibroblasts collected at younger, presymptomatic stages (pre-HD-MSNs) or from age-matched healthy controls. We employed comparative transcriptomics, chromatin accessibility profiling and cellular phenotyping to reveal that HD-MSNs are characterized by marked downregulation of autophagy function compared to pre-HD-MSNs and control MSNs from both young and old age groups. We identify miR-29b-3p, whose marked upregulation in HD-MSNs over pre-HD-MSNs significantly limits autophagy in HD-MSNs via directly targeting STAT3 via human-specific binding sites in the 3' untranslated region (UTR). The autophagy deficiency in HD-MSNs can be overcome chemically or genetically by a glibenclamide analog, G2, or by inhibiting miR-29b-3p, leading to the reduction of mutant HTT aggregation and protection of HD-MSNs from neuronal death. This study provides molecular insights into how aging in HD compromises autophagy in MSNs and its enhancement as a potent approach to increase MSN resilience against neurodegeneration in HD."

Huntington's Disease creates an accelerated aging phenotype. In this paper, a glibenclamide (G2) analog was effective in reversing neuronal death caused by Huntington's. The MOA was enhancement of autophagy.

# Altos Labs Pursing Aging Through Cell Reprogramming

### Greg Zuckerman, Wall Street Journal, August 20, 2023 (excerpt)

The investment firm Robert Nelsen co-founded in 1986, Arch Venture Partners, has racked up billions in profits from early stakes in companies developing methods to detect and treat cancer and other diseases.

Nelsen's latest and largest investment—several hundred million dollars, he says—is in a company attempting something even more ambitious than aiding health and longevity. Altos Labs, based in the San Francisco Bay Area, San Diego, and Cambridge, U.K., is working on ways to rejuvenate cells to eliminate disease—an approach called epigenetic reprogramming. Nelsen and Altos's founders believe they can turn the clock back on aging cells to restore functions characteristic of younger cells.

Arch is the largest institutional investor in Altos, which already has \$3 billion of committed investments, likely making it the biotech industry's best-funded startup on record.

"Epigenetic reprogramming is the biggest thing in healthcare in 100 years. Or ever," he says. "We will clearly live much healthier and longer lives if this works." That's a huge if. Cellular rejuvenation has yet to be proven effective as a treatment. So far, the only data Altos and others in the field have produced is in mice, suggesting they are a long way from rolling out any products. Skeptics doubt cells can be reprogrammed to ward off age-related illnesses. Taking cells back to their youthful, healthier state long captured the imagination of scientists, but seemed unlikely. Then a breakthrough paper published in 2006 by Japanese scientist Shinya Yamanaka and a colleague showed mature skin cells of mice could be reprogrammed into primordial, immature stem cells—called induced pluripotent stem cells—in effect resetting their molecular clocks. Yamanaka, who later shared a Nobel Prize for work in this area, is an adviser to Altos. In 2016, Spanish biochemist Juan Carlos Izpisua Belmonte, Altos's founding scientist, showed how the age of cells could be reverted without changing their genome and identity. His work demonstrated the potential for toggling between the 'old' and 'young' states of cells—the basis for Altos's effort to rejuvenate cells. "If we can turn the clock back so cells are healthy and resilient, you can reverse disease," Klausner says.

But there's limited evidence cellular rejuvenation can be done safely or that it can be an effective way to combat disease or reverse the effects of aging. Some scientists are downright dismissive of the idea. Dr. Richard A. Miller, a professor of pathology at the University of Michigan, who says he hasn't followed Altos's efforts, argues that it's simplistic and misguided to explain illness as the result of cells getting older. In any aging body, cells divide, die, are replaced and change, he notes. So it's unclear if reprogramming cells can ward off sickness, even if it could be done successfully and safely, he says.

"Aging is something that happens to bodies, not to cells," Miller says. "The reprogramming idea seems to be a shortcut to try to make cells 'younger' in the hopes that this will somehow fix everything. There's no evidence this will work."

Others say the approach has both potential and enormous risk.

While Yamanaka's earlier work demonstrates that "cellular reprogramming can reverse the oldness or agedness of cells to take them back to a youthful cellular state in the form of iPS cells," that work was done in cells in a Petri dish in a lab, Knoepfler says. "It's much less clear," he says, if Altos or others can safely reverse the aging of cells and tissues in a person.

Nelsen says he was convinced to bet on Altos by "the breadth of different animal models" demonstrating cell rejuvenation, the quality of the scientists joining the company and the goal of "reversing, not treating disease."

"My goal is not to make a trillion-dollar company," he says. "It's to profoundly restructure a reactive broken industry into a curative industry that has profound impact on humans."

## Aging Drugs Would Dwarf the Obesity Market

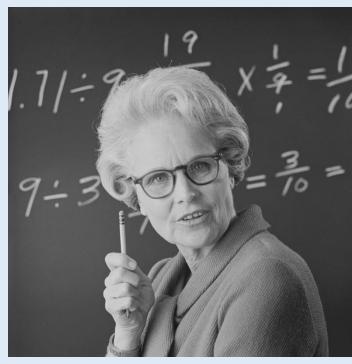
What makes the obesity market so interesting from a financial perspective is the confluence of payor incentives and personal incentives.

The average person is willing to go substantially out of pocket to lose weight and keep it off. Similarly, payors have powerful incentives for population management of weight.\*

It is not difficult to use a spreadsheet and use data on willingness to pay surveys to conclude that, theoretically, the market for a successful obesity drug could exceed \$300 billion – almost ten times the peak sales of drugs seen to date.

We believe that an obesity drug has the potential to become the largest product in human history. iPhone, for example, did \$205 billion in revenue in 2022 and is the highest revenue branded consumer product produced by humanity so far. By comparison, Cheerios<sup>®</sup> revenues are \$18 billion. The math exercise is mind boggling.

We believe that similar incentives would exist in the aging field as seen in the obesity drug market. A drug that extends the healthy human lifespan would be of high interest to both payors and individuals and should elicit an even greater market size than that from an effective weight loss drug – particularly if chronic use would be required to stay alive.



Market sizing math for an effective anti-aging drug is mind boggling.

### Crop Modification is Central to All Civilizations

### Michael Eisen, Ph.D., Professor of Molecular and Cell Biology at UC Berkeley, March 18, 2018

Humans first began collecting and growing edible grains, fruits and roots, and corralling wild animals for meat, milk, and material goods thousands of years ago. Ever since, we have been shaping these plants and animals to meet our needs and desires. Compare corn to its ancestor, teosinte, cattle to the aurochs from which they were derived — or any other crops and livestock on which we rely to their wild relatives — and you'll find the remarkable story of human agriculture and the transformative power of artificial selection.

The success our ancestors had in creating the modern cornucopia of domesticated plants and animals is all the more remarkable for their near-complete lack of understanding of where new traits come from or how they pass from one generation to the next. They didn't know that every trait they favored arose through one or more random alterations — mutations — to a species' genetic code, passed on from parents to their offspring in the form of DNA.

Thus, as much as human history is the history of agriculture, it's also the history of genetic modification of plants, animals and microbes which enabled humanity to overcome the myriad obstacles they faced over the millennia. It is safe to say that, without systemic genetic modification of crops and livestock, civilization would not exist. Humanity now faces a new and daunting set of challenges, with agriculture once again at the center. We have to feed a growing population, but farmers and their crops struggle to adapt to warmer temperatures and altered weather patterns. And livestock, a pillar of our food system for millenia, are major culprits in climate change, water shortages, biodiversity losses and massive degradation and destruction of forests and other ecosystems — compelling us to quickly move to a predominantly plantbased diet.

To meet these challenges, we must employ all of the technological tools at our disposal. This includes our vastly improved understanding of the mechanisms of heredity and the molecular basis for traits that interest us, and powerful new tools that allow us to modify DNA in order to generate specific valuable traits, rather than waiting for them to be delivered by the random winds of mutation.

But the process of genetic modification, central to progress in agriculture throughout history, has become controversial. As a geneticist who uses modern tools for modifying DNA on a daily basis in my research, and who teaches about these methods and the issues surrounding them, I worry that misplaced fears about their use in agriculture will hinder our efforts to address climate change, food insecurity and the degradation of our natural environment.

# Example of a Civilization-Changing Technology: Gene Editing of Crops

- Genome editing allows plant breeders to make changes to plants more quickly and more precisely than through conventional plant breeding methods. It can take plant breeders decades to introduce a new trait into a crop through conventional plant breeding methods, while genome editing has the potential to shorten that timing to a few years.
- Genome editing of crop plants is a rapidly advancing technology whereby targeted mutations can be introduced into a plant genome in a highly specific manner and with great precision. For the most part, the technology does not incorporate transgenic modifications and is far superior to conventional chemical mutagenesis.
- This technology has the potential to profoundly change our civilization impacting many areas including our vulnerability to climate change and food insecurity.
- Climate change imposes a severe threat to agricultural systems, food security, and human nutrition. Gene
  editing of crops can target many relevant phenotypes including attributes that could be beneficial for climate
  change adaptation.
- Gene editing of crops also has high promise to relieve food insecurity. For example, China is relying heavily on this technology to feed its 1.4 billion people.

# Summary

# Bright Future for Biotech

### Summary

As we celebrate the Thanksgiving holiday in 2023 it's clear we have much to be grateful for.

We are all part of an industry that is not just impacting lives but one that promises to change what it means to live in our civilization.

We hope that you share our enthusiasm that medical innovation will positively shape our society and extend life expectancy for humanity in the decades to come.

One of the most remarkable data points in this presentation is the persistent market outperformance of the biopharma sector dating back to 1930.

In general, prices should adjust to reflect opportunities. That is, there is no reason to expect one sector to deliver systematically higher returns than another on a risk-adjusted basis if the market is efficient.

There are only two explanations that we can think of to explain persistent positive return differentials from investment in the biopharmaceutical sector over a period of ninety years.

The first would be that biopharma investments are risker; hence investors require a larger risk premium to enter investments in the sector.

This sounds like it could be true. However, when one looks at the data, the pharma sector has outperformed and has *lower* betas than average. Indeed, according to financial theory, only non-diversifiable risk should be priced

and, on average, biopharma investments have provided a hedge against the overall market and economy.

This is evident in some of the charts in this presentation. For example, it's notable that the pharma sector *rose* in value in the period 1930 to 1934 while the rest of the market dropped in value.

No big surprise. It was the Great Depression and it's remarkable looking back that pharma did so well.

The second explanation is that the growth of profits and expected future profits have consistently exceeded expectations.

We find this explanation to be more palatable. The data shared in this presentation show extraordinary growth of pharma revenue over time. In real terms, U.S. pharma spend has risen over 800 times in the last 90 years. We doubt that market participants along the way anticipated this level of growth. That is, the industry has outperformed expectations, on average, hence the excess returns.

The 64,000-dollar question is whether the industry can be expected to repeat this going forward. Presumably, at some point, one would see expectations catch up to reality. And there is no shortage of industry doubt today. IRA, FTC, you name it.

We can only say that this does not feel like the moment when that has happened. Investors in our industry are negative on the market and sentiment is dour.

The review of the history and prospects for the future would suggest that, if anything, this is a moment to investment with the expectations that historical excess returns can persist.

## Summary (continued)

The confluence of rapid upcoming global growth and the history of what that has meant for pharmaceutical product consumption in the United States paints a very positive picture of what the biopharmaceutical can become in the decades ahead.

The demand side comes with a double dividend that many do not see. Pharma innovation means that, on average, humans will live longer. And, in turn, living longer triggers more demand for pharma products. This creates a positive feedback cycle that should continue to raise pharma spend as a share of GDP over time.

There is high potential for growth in spend on pharma products even in the U.S., where there is high pessimism about the IRA and poor reputation of the pharma industry today.

Most of us are quick to point out the inequities in the IRA to say nothing of the potential risks to industry from using one dimensional cost effectiveness analysis (CEA) to guide future drug pricing conversations.

But few point out that the IRA was passed with a "grand trade" in which copays by Medicare beneficiaries would be capped at a low level. So, yes, the government has a seat at the table on pricing and is a monopsonist.

### Not ideal.

But, on the other hand, the power of the co-pay to limit demand has been almost entirely removed. Particularly for more expensive specialty medicines. It's well known that many patients are not buying drugs when they should be. In private conversations, some pharma executives have speculated to us that the IRA could end up being a net positive.

A further factor to consider in the U.S. is the fact that drug price negotiations are political. That is, it is entirely possible that future Presidents might be more conservative and more pharma friendly than the current one. The President nominates the head of HHS, and the head of HHS determines how dogged the government will be in price negotiations. Or whether it tries at all.

We are not saying that the IRA is benign. But we wish to note that it's future degree of harm to the pharma sector is far from determined. In contrast, the change in copay rules is *hard wired* into statute.

Add this to a period of extraordinary ongoing drug discovery linked to an increased understanding of genetics and biology and we are poised to see countless new innovations make their way to patients.

When coupled with the explosion of progress in our ability to efficiently develop and discover drugs across so many interesting modalities, we are likely to see a meaningful uptick in therapeutic options for patients in need.

We have argued herein that biologic innovation has been civilization changing for millennia and will continue to be for many more. The opportunities to impact human civilization with upcoming innovation in biology is awe inspiring.

Buckle up and let's go! We have an amazing bioscience century in front of us.



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