LifeLink Ventures

2022

Annual Biotech Report

We wish to connect private investors with emerging technologies that address global health challenges. To do so, first we must bring our investors closer to the biotech world

Foreword

"We're excited to be a part of LifeLink and support this next phase of its journey."

Ricardo Salomão, LifeLink Partner & Green Rock General Partner

We are pleased to welcome a new and experienced partner into our LifeLink family – Green Rock.

In 2017, families Salomão and Zoppi co-founded Green Rock as their investment office after 36 years of successfully building one of the biggest diagnostics labs in Brazil - SalomaoZoppi Diagnostics - and selling it to Dasa Group. Alongside a successful business, over the last 40 years Salomão and Zoppi built an inspiring partnership deeply rooted in trust and respect.

Today, their investment office Green Rock focuses on 3 major segments: real estate, venture capital and private equity. With their background and expertise in the health sector, the families decided to focus their investments on healthcare. As such, Green Rock is one of the most active and well-known investment offices in Brazil dedicated to the healthcare sector.

Given the great alignment with LifeLink, not only in investment areas but most importantly in core values, Green Rock has joined forces with LifeLink in 2022.

We are delighted to count on their experience, guidance and support and look forward to building a successful business, side by side.

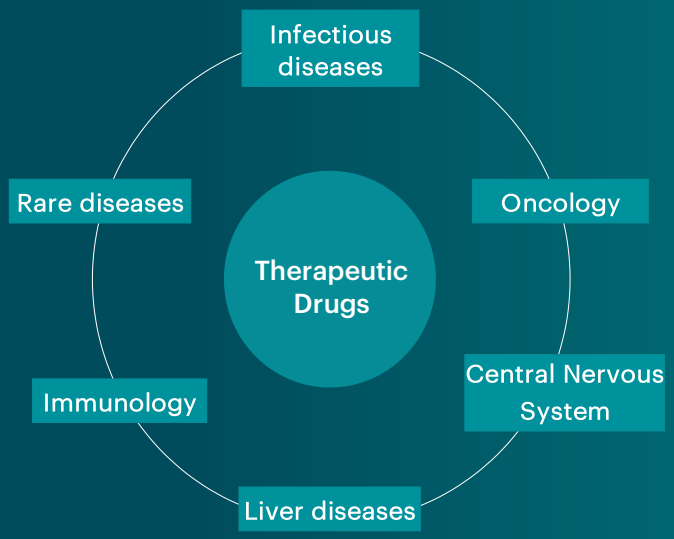
Ricardo Salomão, MD
Green Rock General Partner
& LifeLink Partner

Francisca Peixoto, PhD, MBA
Founding Partner &
Managing Partner

Leo Figueiredo
Founding Partner &
Executive Chairman

LifeLink Ventures

LifeLink Ventures is focused on impact investing through life sciences. Our primary focus is therapeutic drug development for diseases with high unmet medical needs:



Current LifeLink Portfolio Areas

Oncology
- Brain cancer

Rare diseases
- Hemophilia

Infectious diseases
- Shigella & E. coli infections

Liver diseases
- Liver transplantation

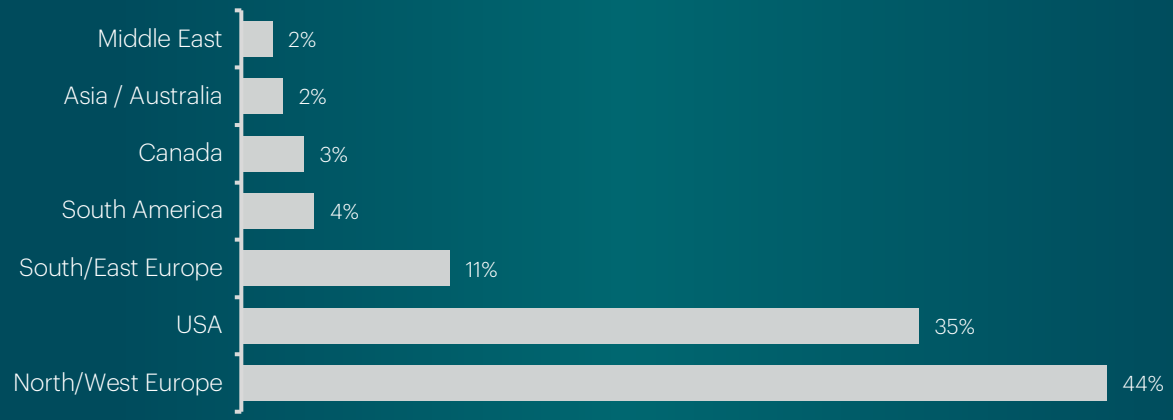
Central nervous system
- Neurodegeneration

Immunology
- Asthma and inflammation

Our portfolio companies are committed to solving global health issues. Detailed descriptions include, **InCephalo Therapeutics** developing immune oncology therapies for brain cancer; **Ochre Bio** developing RNA therapeutics for liver transplantation; and **Accure Therapeutics** developing new treatments for epilepsy and Parkinson's.

We broadly source innovative science and technology from Europe and USA with an expanding presence worldwide, to explore additional areas including cardiovascular and autoimmune disorders while identifying complementary companies in the above areas of drug development.

2022 Geographic Sources of LifeLink Deal Flow



2022 Annual Biotech Report

Highlights

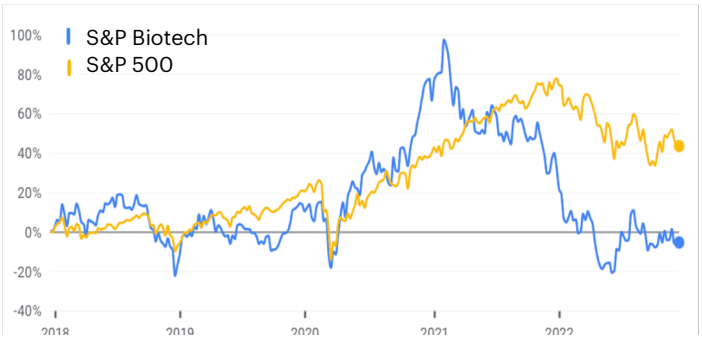
LifeLink

1. Biotech in 2022

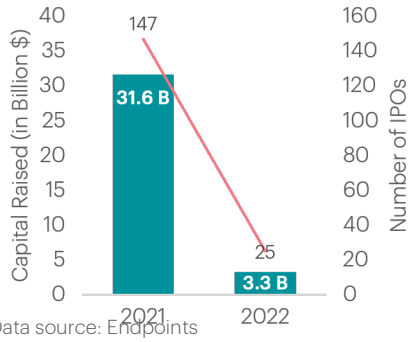
Public Markets

At the start of 2022, biotech stocks plummeted and twelve months later, IPOs are almost non-existent. Since late 2021, the biotech market has lost over 40% of its value, with some clinical companies losing over 80% of their market cap after disappointing clinical readouts.

S&P 500 and S&P Biotech stock price over the last 5 years



Number and value raised In biotech IPOs



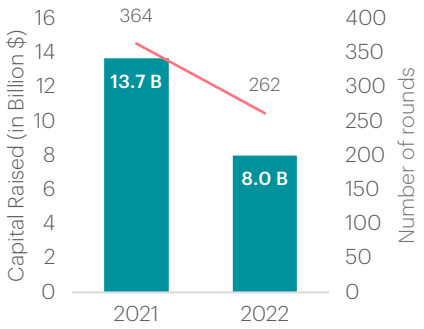
Data source: Endpoints

While the market was likely overinflated in 2021, prices have also suffered due to Covid-19 "tourist" investors leaving the market and macroeconomic uncertainties, including the Russian invasion of Ukraine. Consequently, the **number of biotech IPOs has decreased almost 6x** in comparison to 2021 and capital raised in 2022 was barely over 10% of 2021 values.

Venture Funding

Global venture funding also fell through 2022, with late-stage suffering most (64% down), as few biotech companies are making it to public markets. Even large market areas including cancer saw declines in funding.

Global Venture Funding to Cancer Startups

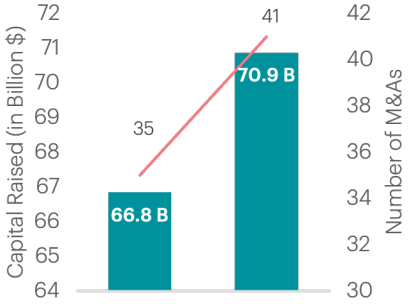


Data source: Crunchbase

Mergers & Acquisitions

Regardless of these difficulties, the industry has been busy on the M&A front. Several big pharma companies were flush with cash leading into the year, thanks to top-selling COVID-19 products, innovative branded medications, and high-value divestitures. In short, M&A activity was characterized by a **sizable uptick in the number of buyouts** and similar average deal size ($1.8 Billion) for deals over $50M relative to 2021.

Number and value deployed in biotech M&As over $50M



Data source: BioPharma Dive

Opportunity

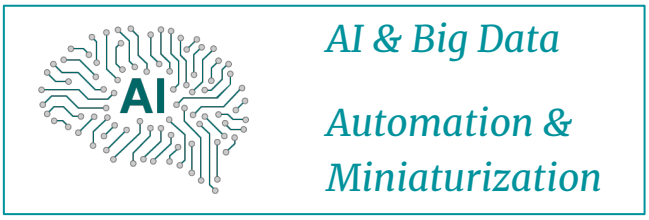
2022 brings a strong and likely needed correction to valuations. Corrections are a natural part of investing, and although every cycle is unique, they pose remarkable opportunities to invest in innovation at adjusted prices.

2. Opportunities in Artificial Intelligence

Tech enabled biotech

The most important value inflection point for a biotech is proof of human efficacy. Over time biotechs have adapted tools to reduce the time to these milestones. To further decrease drug discovery and development timelines, the industry is leveraging new software and hardware.

"The use of artificial intelligence and machine learning could lead to an additional 50 novel therapies over a 10-year period ... a $50 billion opportunity" (Morgan Stanley, 2022)



In terms of software, artificial intelligence has improved the ability to identify new drivers of disease from multiple levels of genetic information while computationally predicting chemical compositions of new drugs. In terms of hardware, robotic automation and miniaturization have increased the scale, by order of magnitude, at which small teams can conduct experiments in parallel. Notably, the data produced from hardware can iteratively improve software predictions.

As of 2022 a handful of A.I. developed drugs are in clinical trials and the coming years will be key initial inflection points assessing the ability of A.I. to speed up drug development timelines.

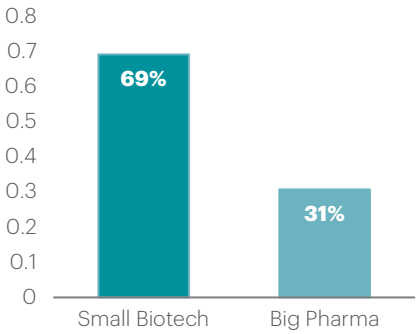
3. Small Biotech-A Key Source of Innovation

Small biotech vs big pharma

The current business model for drug development often includes big pharmaceutical companies outsourcing pre-clinical research and development to small or mid-sized biotech companies. Following sufficient proof of concept, frequently in patients, pharmaceutical companies will acquire whole companies or individual products.

To highlight the critical importance of biotechs on drug development, we analyzed the source of all FDA approved drugs in 2021 and 2022. As displayed in the graph, out of the 78 drugs approved in the past two years, 69% of them originated from small or mid-sized biotechs, while 31% came directly from large pharma companies. This demonstrates that **biotechs are effectively required to maintain and drive innovation in drug development.**

Origin of FDA approved drugs 2021 - 2022



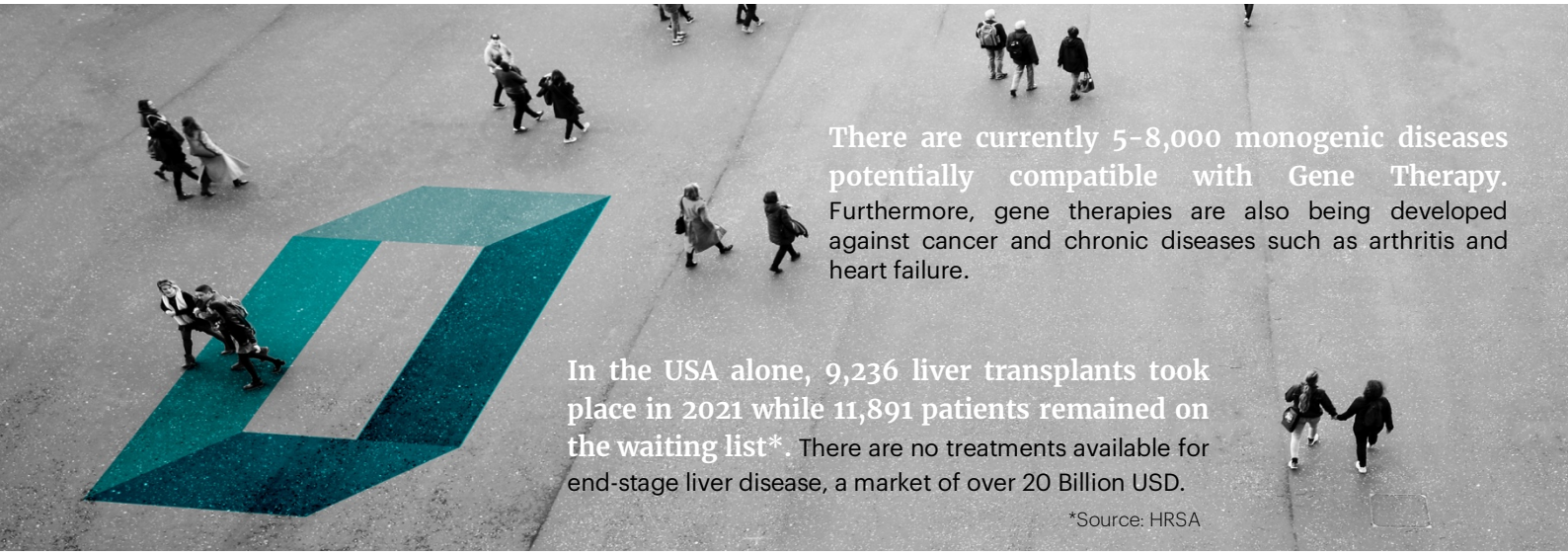
4. LifeLink Areas of Interest

Gene Therapies

Gene therapies deliver whole genes to specific organs to cure patients afflicted by various diseases (frequently genetic diseases). While the potential of the technology is immense, concerns over side effects and therapeutic durability often prevents therapies from entering the market.

2022 was a landmark year, as newly approved gene therapies for hemophilia and cancer are poised to test, for the first time, if gene therapies can scale to the demands of large patient populations and compete with established standards of care.

LifeLink portfolio company **Chameleon Biosciences** continues their mission to dramatically broaden the qualifying patient population by circumventing aspects of immune surveillance that limits many gene therapies to a single dose in upwards of half of adult patients across all diseases.



Liver Disease

This year, Madrigal Pharmaceuticals reported positive results in a large Phase III clinical study for a common type of liver disease named NASH. In an industry littered with setbacks, the announcement sets the stage for **the potential first NASH drug approval** by the FDA.

Due to patient heterogeneity, liver disease is a challenging area for drug development, often requiring large and costly clinical trials. Madrigal reported disease improvements in 25% of patients, a result described as “significantly exceeding expectations” by an analyst at SVB Securities. While this study increases confidence, there is still an obvious need for additional and improved liver disease therapeutics.

LifeLink portfolio company **Ochre Bio** continues their mission to build the most detailed genetic map of liver disease progression while redefining the methods of liver disease drug development.

5. 2022 Stories

FDA Leniency

Two drugs have strengthened criticisms that the FDA is taking an increasingly lenient position when evaluating drugs for neurodegenerative disease: In 2021 the FDA approved the Alzheimer's drug Aduhelm™, through an accelerated process relying on biomarkers over efficacy (further discussed in Section 6). However, due to limited real-world evidence of patient benefit, **Aduhelm™ has been poorly adopted by clinicians and insurance payers through 2022.**

In 2022, the FDA approved the ALS drug Relyvrio™, based on limited benefits to a clinical score measuring ALS symptom progression. In an unusual process, the FDA held an irregular advisory meeting after an initial committee voted down the drug. While the data presented was reportedly identical, the second committee strongly supported approval. ALS advocacy groups have supported the approval; however, some clinicians worry that such behavior **may lead to the prescription of ineffective drugs and damage patient trust in the drug approval process**.

Precision Medicine

Precision medicine uses patient genetics to guide the development of new therapeutics. Oncology is specifically moving towards a future where drug regimens are tailored designed to a patient's genome. 2022 saw the **approval of a breakthrough precision lung cancer drug** Krazati™ that specifically activates in cancer cells with a genetic mutation known to aggressively drive cancer progression. In addition to preferentially killing cancer cells, precision drugs hold promise of strong safety profiles as they are designed to be largely inactive in normal cells.

mRNA Cancer Vaccines

Cancer vaccines aim to educate the immune system to specifically recognize and kill cancer cells. While cancer vaccines hold great promise, no cancer vaccine has been approved by the FDA yet.

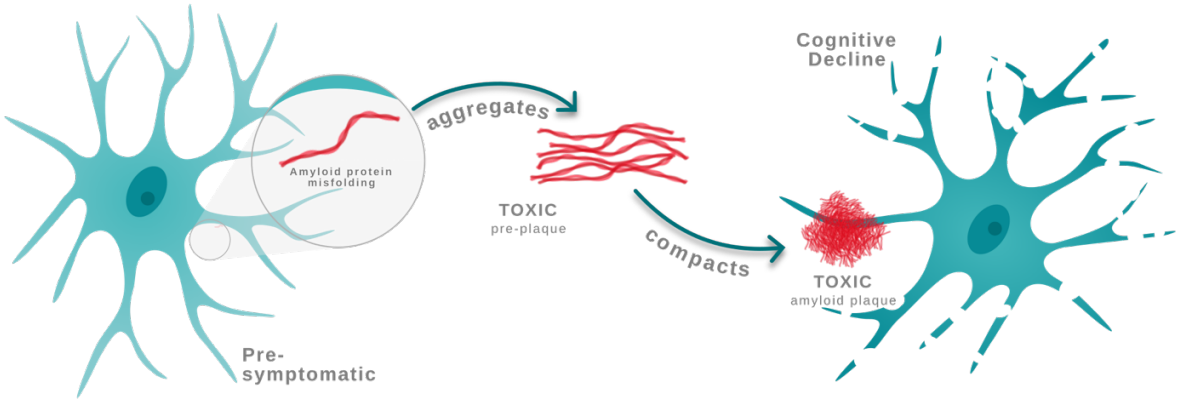
In 2022, mRNA vaccine leader Moderna reported that their **personalized mRNA cancer vaccine reduced the risk of melanoma recurrence in late-stage patients by 44%**. The innovation of this vaccine lies in that Moderna designs each vaccine based on unique patient tumor genetics from individual biopsies. The application of mRNA to cancer vaccination specially pairs well with personalization, as the sequence of RNA can more easily be tailored and updated to individual patients at scale. Moderna will continue the development of this vaccine in late-stage clinical trials, with their pharmaceutical partner Merck.

6. Alzheimer´s Breakthroughs

Clinical Landscape

The amyloid hypothesis predicts that an underlying cause of Alzheimer's disease is the gradual accumulation of toxic protein aggregates in the brain, referred to as **amyloid plaques**. While the hypothesis is longstanding, **plaques have yet to be shown to functionally cause cognitive decline**.

Amyloid Hypothesis:



Efficacy and Safety

Following the discovery of the correlation between amyloid plaque accumulation and Alzheimer's symptoms, tremendous scientific effort has been focused on developing drugs that remove amyloid plaques in early patients. **In 2021, the first Alzheimer's treatment able to remove plaques was approved,** and several other amyloid-focused treatments are in development.

Company	Therapeutic	Modality	Stage	Efficacy
Biogen	Aducanumab (Aduhelm™)	Antibody	Approved (2021)	Positive results in plaque reduction No results in cognitive score
Biogen & Eisai	Lecanemab (Leqembi™)	Antibody	Approved (2023)	Positive results in plaque reduction Positive results in cognitive score
Eli Lilly	Donanemab	Antibody	Phase 3	Positive results in plaque reduction
Roche	Gantenerumab	Antibody	Phase 3	No observed benefits. Halted clinical development.
Alzheon	ALZ-801	Small Molecule	Phase 2	Positive results in cognitive score

Because Aduhelm™ was approved through an accelerated process based on amyloid plaque clearance, cognitive benefit has yet to be demonstrated. In a first of its kind readout, **Lecanemab recently reported measurable reductions in the rate of cognitive decline** in early patients, further supporting the "amyloid hypothesis".

In terms safety, multiple antibodies increase the incidence of cerebral imaging abnormalities, which are associated with an elevated risk of brain micro-hemorrhaging and may have been the possible cause for three reported deaths (which are still under investigation) of Lecanemab clinical trial participants. Nonetheless, just at the start of 2023, **Lecanemab has effectively been approved by the FDA**, becoming the second approved Alzheimer's treatment.

Future Perspectives

Alzheimer's is a complex and highly heterogenous disease. While finding a single cure for all cases is unlikely, the accumulation of clinical data, additional therapeutic approaches (not discussed in this report) and numerous ongoing clinical trials bring humanity closer than ever to generating effective treatments for an incredibly elusive form of neurodegeneration.

7. Contact

For more information on LifeLink Ventures or our portfolio companies please reach out or visit our webpage:

Webpage: www.lifelinkventures.com
Email: info@lifelinkventures.com
Company: LifeLink Ventures Limited
Location: Barcelona, Spain

LifeLink Ventures