FRANKLIN TEMPLETON

Franklin Biotechnology Discovery Fund

United States - Retail

Advisor Class
Class A
December 31, 2024

Product Commentary

Performance Review

- During the fourth quarter of 2024 (4Q24), global stocks were pressured by investor concerns about economic growth, persistent inflation in some regions and the likelihood of further interest-rate cuts in 2025. While Donald Trump's presidential victory and the potential for additional tax cuts and expansionary fiscal policy supported US equities, investors outside the United States were concerned about the president-elect's tariff plans and their implications on global trade. As measured by MSCI indexes in US-dollar terms, developed market equities fared better than a global index, while emerging market equities underperformed it. Seven out of 11 equity sectors sold off globally in 4Q24, with health care near the bottom of the pack with a 10th-place finish. The biotechnology, pharmaceuticals, and life sciences tools and services industries were among the worst performers; all three sustained overall losses in the 12% to 13% range, though health care providers and services fared worse, while health care technology was the only industry-level outlier to the upside. Sector rotation out of health care was attributable to several factors as investors generally reallocated funds away from health care to potentially capitalize on the more cyclical areas of the economy, including (1) ongoing regulatory uncertainty affecting drug pricing and approval processes; (2) health care costs, including labor and materials, which have been rising faster than general inflation (thereby squeezing profit margins for many health care companies); (3) health care spending that has been growing at a slower pace compared to the overall economy; and (4) perceived risks around the potential impacts on health care by President-elect Donald Trump's new administration and proposals. Trump is expected to focus on deregulation and policy rollbacks, which includes modifying or reversing outgoing President Joe Biden's policies. These issues have created uncertainty, particularly for biotechnology and pharmaceutical companies. The incoming administration also plans to promote market competition and transparency to help improve access to health care and reduce costs. However, there are concerns about potential cuts to public health insurance programs and the introduction of work requirements for Medicaid. With advisors like Robert F. Kennedy Jr., who is skeptical of vaccines, there is apprehension about changes to public health interventions. This could impact investor confidence in companies involved in vaccine production and public health campaigns. The specifics of all these policies are still unclear, leading to investor caution. The biotech industry logged a record number of US Food & Drug Administration (FDA) drug approvals in 2023, which could potentially drive revenue expansion for the respective companies for a decade or more; the industry set a similar pace in 2024 as 50 FDA novel drug therapies were approved (versus 55 for all of 2023). And the pace of innovation continues, with companies reporting clinical progress for the next wave of medical advances in cancer, neuromuscular disease and autoimmune conditions. In medical devices, pulsed field ablation is emerging as a new paradigm for addressing atrial fibrillation (a type of irregular heartbeat) that is safer and faster than prior methods. Meanwhile, the adoption of robotic surgery is allowing procedures to be completed with more accuracy, less pain, faster recovery times and better outcomes. And the latest robotic surgery systems have 10,000 times the processing speed of prior generations. Many more examples exist throughout the sector, with important clinical trial and product updates expected in the months to come for cancer, obesity, lupus and schizophrenia.

QUARTERLY KEY PERFORMANCE DRIVERS

	Stocks	Industries
HELPED	UniQure (Significant Overweight)	Health Care Services (Overweight, Stock Selection)
	Arcutis Biotherapeutics (Significant Overweight)	—
	Benitec BioPharma (Off-Benchmark Exposure)	—
HURT	Gilead Sciences (Underweight)	Pharmaceuticals (Stock Selection)
	Applied Therapeutics (Significant Overweight)	Biotechnology (Stock Selection)
	Alto Neuroscience (Off-Benchmark Exposure)	Health Care Equipment (Lack of Exposure)

- The fund had negative absolute and relative returns in the biotechnology (averaging 77.9% of total net assets) and pharmaceuticals (14.3% of total assets) industries. Within pharmaceuticals, benchmark or overweighted investments in key detractors Alto Neuroscience, Marinus Pharmaceuticals (not held at period-end) and Revance Therapeutics (not held at period-end) suffered large double-digit percentage losses. Alto and Marinus shed more than half of their equity values after they revealed disappointing clinical trial results. On October 22, Alto announced that its Phase 2b study of ALTO-100, aimed at treating major depressive disorder (MDD), did not meet its primary endpoint. Alto is still actively developing several drugs and therapies, focusing on innovative approaches to mental health conditions. Revance is a clinical-stage biotech focused on novel botulinum toxin products for multiple aesthetic and therapeutic applications, including the production of daxibotulinumtoxinA, a cultured botulinum toxin branded as DAXXIFY, for aesthetic and therapeutic indications including facial wrinkles and muscle movement disorders. Revance reported quarterly earnings that fell short of consensus analyst expectations. Additionally, in light of uncertainties surrounding a proposed merger with Crown Laboratories (not held by the fund) and other recent developments, Revance did not provide any forward-looking guidance and withdrew any previous guidance or outlook. Revance and Crown announced that they had entered into a merger agreement a few months ago, but there were delays as the two parties come to terms with the specifics, thereby unintentionally extending the deadline to close the deal.
- All of the other key 4Q24 detractors versus the NASDAQ Biotechnology Index were in the fund's core biotech allocation. Aside from underweighted detractor Gilead Sciences (which advanced) and a lack of exposure to several index-component companies that rallied (i.e., Scholar Rock Holding, Exelixis and Madrigal Pharmaceuticals), there was a fairly long list of overweighted or off-index portfolio holdings that sustained double-digit percentage losses, including Applied Therapeutics, Achieve Life Sciences, Keros Therapeutics, Vaxcyte, Kura Oncology and Olema Pharmaceuticals (purchased during the period). Applied Therapeutics, a clinical-stage drug developer targeting treatments for central nervous system rare diseases and diabetic complications, shed most of its equity value in a dramatic decline primarily due to the FDA issuing a Complete Response Letter (CRL) for the company's New Drug Application (NDA) for govorestat, a drug intended to treat classic galactosemia (a genetic disorder affecting galactose metabolism). The CRL indicated deficiencies in the clinical application, meaning the drug was not ready for approval in its current form. Afterward,

Applied Therapeutics' chief executive officer (CEO) provided what we would describe as transparent answers, stating that there was no mention of risk, benefit, adverse liver signals, irregularities in CMC (chemistry, manufacturing and controls), or non-clinical data as reasons for not approving. If we believe the CEO's characterization of the CRL, the most likely explanation is that the failed primary endpoint in the clinical outcome portion of the Phase 3 trial was enough to cause the FDA to doubt the "substantial evidence of efficacy" despite the supportive secondary endpoints and unmet need around a rare disease. The company was in discussion with the FDA to better understand the path forward in galactosemia and will likely provide an update to investors in January. We continue to hold the stock as this discussion unfolds, and as the company remains on track to file for FDA approval in other areas, including the application of govorestat for the treatment of sorbitol dehydrogenase deficiency in early 2025. Keros, meanwhile, encountered unexpected safety concerns in its Phase 2 TROPOS trial for cibotercept, a treatment for pulmonary arterial hypertension. The trial was halted for the two highest doses after reports of excess fluid buildup in the pericardial sac around the heart. This unanticipated setback led to a loss of investor confidence, as cibotercept was the company's lead program and main value driver. The trial will continue with the lowest dose, but we believe it will take more data to regain investor trust.

- In terms of key contributors, an overweighted stake in Guardant Health, our sole holding in health care services, helped the fund outperform the index in that industry. Guardant focuses on cancer treatment through advanced diagnostics, providing a range of blood and tissue tests, data sets, and analytics to help with treatment selection, recurrence detection and early detection. In short, Guardant is seeing exceptional demand for its products. As a result, the company reported 3Q24 earnings that significantly exceeded consensus analyst expectations. Its revenue saw a 34% increase from the previous year, driven by a 21% rise in clinical tests and a 40% increase in biopharma tests. Guardant raised its full-year revenue guidance to $720 million–$725 million, up from the previous forecast of $690 million–$700 million. In the biotech industry, several overweight or off-benchmark holdings posted solid rallies, led by UniQure, Arcutis Biotherapeutics, Benitec Biopharma, PTC Therapeutics, Praxis Precision Medicines, Neurocrine Biosciences and Argenx. Among these positive outliers, UniQure's share value surged more than threefold, primarily due to positive developments regarding its gene therapy candidate, AMT-130, for Huntington's disease. The company announced that the FDA would consider an application for accelerated approval based on ongoing Phase 1/Phase 2 clinical trials. This unexpected news significantly boosted investor confidence, driving the stock price substantially higher. The gain for Arcutis was also impressive as its equity value increased by roughly 50%. The company, which develops treatments for unmet needs in immune-mediated diseases and conditions, reported robust 3Q24 financial results, with a notable 45% increase in revenue compared to the previous quarter. This growth was driven by strong demand for ZORYVE (roflumilast) products, which address a range of chronic skin conditions. Arcutis received Health Canada approval for ZORYVE foam for seborrheic dermatitis and had a supplemental NDA accepted by the FDA for the treatment of scalp and body psoriasis. These regulatory milestones boosted investor confidence. We maintain a positive sentiment on Arcutis as its versatile ZORYVE products offer patients steroid-free options that are well-tolerated and convenient, while the company continues to expand its market presence, with plans to launch new products and expand into additional therapeutic areas. Praxis, meanwhile, is a clinical-stage biopharmaceutical company engaged in genetic epilepsies and the development of therapies for central nervous system (CNS) disorders characterized by neuronal excitation-inhibition imbalance. It announced progress in its clinical pipeline, including the upcoming interim analysis for ulixacaltamide in essential tremor, expected in early 2025. We note that the company maintains what we view as a solid financial runway into 2027, reassuring investors about its ability to fund ongoing and future clinical trials. Benitec was another exceptional contributor as its share price increased significantly. Benitec is a clinical-stage company that focuses on developing novel genetic medicines using a proprietary platform called deoxyribonucleic acid (DNA)-directed ribonucleic acid (RNA) interference (ddRNAi). This platform combines RNAi with gene therapy to create treatments that can "silence" disease-causing genes with a single administration. Benitec is working on ddRNAi-based therapeutics for chronic and life-threatening conditions, including oculopharyngeal muscular dystrophy (OPMD). The company's stock rally was primarily due to positive December updates and greater investor awareness of its OPMD programs. In the pharmaceuticals industry, overall losses were substantially reduced by solid gains for our two largest holdings therein: Intra-Cellular Therapies and Jazz Pharmaceuticals. Intra-Cellular's stock preached a record high after it reported a consensus-topping batch of quarterly financial data, with 3Q24 sales for psychiatric drug Caplyta of $175.4 million coming in above the consensus estimate of $172 million, driven by continued strength in bipolar depression-related demand. The company's forward guidance was raised and the range narrowed accordingly. Importantly, the company recently filed a supplemental NDA with the FDA for Caplyta for the treatment of MDD in adults, as an adjunctive therapy to antidepressants, based on solid results from two clinical trials.

Outlook & Strategy

- **The portfolio continues to be overweighted in mid-, small- and micro-capitalization biotechnology stocks** as these market-cap tiers are where we see some of the best value. We also continue to emphasize selectivity, favoring what we believe to be clinically or commercially "derisked" assets.
- **Our positive outlook is based on what we consider to be generally strong fundamentals and appealing valuations backed partly by innovation in new drug modalities,** an accommodative FDA, the resumption of what we see as a strong merger-and-acquisition (M&A) cycle, and relatively stable Medicare drug reimbursement.
- **Conversely, we remain cognizant of risks to biopharma innovation and stock performance** linked to the persistence of inflation and the potential for only minimal interest-rate reductions in the United States in 2025. We are also concerned about a worse-than-expected 2025 impact from the implementation of Inflation Reduction Act (IRA) drug pricing measures in the United States. That said, we don't want to overstate the risk because the IRA pertains to US revenues and only Medicare revenues therein, which means drugs that skew towards older populations.
- **The current US drug reimbursement scenario is undergoing significant changes, particularly with the introduction of new models for cell and gene therapies (keeping in mind that gene therapy investments are a relatively small percentage of the health care sector and the fund's portfolio mix).** The US Centers for Medicare & Medicaid Services has proposed increasing the new technology add-on payment for these therapies, which could potentially improve the profitability of biotech companies involved in developing such treatments. Moreover, the industry is also facing challenges due to dynamic pricing pressures and the need for novel payment mechanisms that reflect the full value of transformative therapies. While there are efforts to improve the reimbursement landscape for innovative therapies, which could benefit biotech companies, there are also significant challenges that could impact profitability. The industry must navigate these changes carefully to maintain a balance between innovation, patient access and financial sustainability.

- **Big drugmakers want to deepen their product pipelines as the approaching "patent cliff" and policies linked to the IRA threaten a portion of their future revenues, with an estimated US$200 billion in annual patent-related revenue at risk through 2030.** The Medicare Drug Price Negotiation Program embedded in the IRA legislation could cause a big drop in the prices at which drugs are reimbursed, creating a "functional" patent expiration. These dynamics are increasingly driving large pharma companies' ambitions to fill looming revenue holes through bolt-on acquisitions of late-stage drug developers and commercial biotech companies.
- **The recent uptick in health care sector M&A activity could potentially continue to provide a tailwind** as capital constraints put pressure on smaller or early-stage companies and intensifying drug reimbursement pressures and patent-exclusivity losses impact larger commercial enterprises. We anticipate an industry consolidation-driven inflection point resulting from these pressures. These and other market-volatility factors hold the potential to increase the cost required to develop new products and could have significant implications for commercial and portfolio strategies going forward.
- **Biotech IPO (initial public offering) volume is improving but still isn't where it was before the 2022–2023 biotech stock downturn.** In conjunction with depressed private equity and venture capital funding, biotech remains in a rough patch as investors are holding out for more proof-of-concept and clinical trial results. We believe these capital constraints are leading small-cap and start-up companies to seek funding and growth opportunities through other avenues, such as M&A activity with larger firms.
- **The road ahead for biotechnology and pharmaceuticals may be different from that of prior years, but these industries are not lacking innovation prospects despite consolidation.** We are enthusiastic about progress in the areas of radiopharmaceuticals and antibody drug conjugates. We also see how further progress in the fields of cell therapy, gene therapy and gene editing can allow the industry to address diseases in areas of significant unmet medical need. GLP-1 (glucagon-like peptide-1) agonists and weight-loss treatments are another area of interest as the consumer fervor around these drugs rapidly expanded the market in 2023, with sales accelerating again in 2024. Recent shortages of these novel diabetes and obesity medications have been largely resolved, and they are now more widely available than ever.
- **Alongside the biotech and pharma spheres, we are encouraged by what we are seeing in background processes, as novel discovery tools and the adoption of artificial intelligence (AI) and machine learning (ML) technologies are enabling faster and more rational drug discovery and development.** While still in the early stages, the adoption of AI/ML tools in drug discovery is expected to grow rapidly in the near term. We believe AI/ML offers the potential to identify novel targets that were previously thought to be "undruggable," as well as improve drug design by simulating molecular behavior and interactions.
- **We believe that, over the long term, investment in the biotechnology industry should lead to a potentially strong performance.** The biopharmaceutical business model benefits from wide intellectual property moat (i.e., competitive advantage over other firms), strong pricing power and high profit margins. Global pharmaceutical expenditures are growing at an above-GDP (gross domestic product) rate and are relatively insulated from fluctuations in the business cycle. This is supported by the ageing of developed country populations and the dynamic that older individuals consume far more pharmaceuticals than younger ones. Lastly, innovative new drug platforms and technologies are broadening the market opportunity in areas that still have significant unmet medical needs, outpacing the loss of revenues to patent expirations and legislated price cuts.

Fund Details

Inception Date	09/15/1997
Benchmark	NASDAQ Biotechnology Index, S&P 500 Index

Fund Description

The fund seeks capital appreciation by investing at least 80% of its net assets in securities of biotechnology companies and discovery research firms including those involved in fields such as genomics, genetic engineering, and gene therapy, as well as health care, pharmaceuticals and agriculture.

Performance Data

Average Annual Total Returns[1] (%)

	1 Mth	3 Mths	1 Year	3 Year	5 Year	10 Year	Since Inception	Inception Date
Advisor Class - With Sales Charges[a,b]	-6.47	-10.59	4.26	2.72	3.09	3.35	9.72	09/15/1997
Advisor Class - Without Sales Charges[a,b]	-6.47	-10.59	4.26	2.72	3.09	3.35	9.72	09/15/1997
Class A - With Sales Charges[a]	-11.63	-15.57	-1.72	0.54	1.67	2.52	9.33	09/15/1997
Class A - Without Sales Charges[a]	-6.50	-10.66	4.00	2.46	2.83	3.10	9.56	09/15/1997
NASDAQ Biotechnology Index	-7.19	-9.59	-1.37	-3.04	2.63	3.10	9.98	-
S&P 500 Index	-2.38	2.41	25.02	8.94	14.52	13.10	9.01	-

Performance data quoted represents past performance, which does not guarantee future results. *Current performance may be lower or higher than the figures shown. Principal value and investment returns will fluctuate, and investors' shares, when redeemed, may be worth more or less than the original cost. Performance would have been lower if fees had not been waived in various periods. Total returns assume the reinvestment of all distributions and the deduction of all fund expenses. Returns with sales charge reflect a deduction of the stated maximum sales charge. Returns for periods of less than one year are not annualized. All classes of shares may not be available to all investors or through all distribution channels. For current month-end performance, please call Franklin Templeton at (800) DIAL BEN/(800) 342-5236 or visit www.franklintempleton.com.*

An investor cannot invest directly in an index, and unmanaged index returns do not reflect any fees, expenses or sales charges.

Share Class Details

			Sales Charges		Expenses	
	CUSIP	Ticker	Max	CDSC	Gross	Net
Advisor Class	354713398	FTDZX	–	–	0.81%	0.80%
Class A	354713844	FBDIX	5.50%	–	1.06%	1.05%

The **NASDAQ Biotechnology Index** is a modified capitalization-weighted index designed to measure performance of all NASDAQ stocks in the biotechnology sector. Source: Nasdaq OMX.

The **S&P 500 Index** features 500 leading U.S. publicly traded companies, with a primary emphasis on market capitalization. Source: © S&P Dow Jones Indices LLC. All rights reserved.

Portfolio Diversification

Top Equity Issuers
% of Total

Top Holdings	%
AMGEN INC	6.13
VERTEX PHARMACEUTICALS INC	5.81
GILEAD SCIENCES INC	5.69
REGENERON PHARMACEUTICALS INC	5.58
INTRA-CELLULAR THERAPIES INC	3.73
ARGENX SE	3.44
JAZZ PHARMACEUTICALS PLC	3.35
NEUROCRINE BIOSCIENCES INC	2.86
ASTRAZENECA PLC	2.77
MERUS NV	2.64

Investment Team

Evan McCulloch, CFA
Years with Firm 32
Years Experience 33

Akiva Felt
Years with Firm 6
Years Experience 17

1. Periods shorter than one year are shown as cumulative total returns.

What Are The Risks?

All investments involve risks, including possible loss of principal. The portfolio is **non-diversified** and may invest in a relatively small number of issuers, which may negatively impact the fund's performance and result in greater fluctuation in the value of the fund's shares. To the extent the portfolio invests in a **concentration of certain securities, regions or industries,** it is subject to increased volatility. **Small- and mid-cap stocks** involve greater risks and volatility than large-cap stocks. **International investments** are subject to special risks, including currency fluctuations and social, economic and political uncertainties, which could increase volatility. These risks are magnified in **emerging markets**. The manager may consider **environmental, social and governance (ESG) criteria** in the research or investment process; however, ESG considerations may not be a determinative factor in security selection. In addition, the manager may not assess every investment for ESG criteria, and not every ESG factor may be identified or evaluated. These and other risks are discussed in the fund's prospectus.

Important Information

The information provided is not a complete analysis of every material fact regarding any country, market, industry, security or fund. Because market and economic conditions are subject to change, comments, opinions and analyses are rendered as of the date of this material and may change without notice. A portfolio manager's assessment of a particular security, investment or strategy is not intended as individual investment advice or a recommendation or solicitation to buy, sell or hold any security or to adopt any investment strategy; it is intended only to provide insight into the fund's portfolio selection process. Holdings are subject to change.

Before investing, carefully consider a fund's investment objectives, risks, charges and expenses. You can find this and other information in each prospectus, or summary prospectus, if available, at www.franklintempleton.com. Please read it carefully.

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a. Gross expenses are the fund's total annual operating expenses as of the fund's prospectus available at the time of publication. Actual expenses may be higher and may impact portfolio returns. Net expenses reflect contractual fee waivers, expense caps and/or reimbursements, which cannot be terminated prior to Fee_Waiver_Effective_Date without Board consent. Additional amounts may be voluntarily waived and/or reimbursed and may be modified or discontinued at any time without notice.
b. Performance quotations for this class reflect the following methods of calculation: a) For periods prior to the fund's Advisor Class inception date, a restated figure is used based on the fund's oldest share class, Class A performance, excluding the effect of Class A's maximum initial sales charge but reflecting the effect of the Class A Rule 12b-1 fees; and b) for periods after the fund's Advisor Class inception date, actual Advisor Class performance is used, reflecting all charges and fees applicable to that class.

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