Franklin Biotechnology Discovery Fund

Franklin Templeton Investment Funds

A (acc) USD
30 September 2021

FRANKLIN TEMPLETON

Fund Commentary

Performance Review

- Global equity markets edged down during 2021's third quarter on mixed underlying results as a selloff in September erased the earlier gains of many markets. Throughout the summer, many investors were pricing in the potential for the US Federal Reserve to begin tapering stimulus sooner than expected. Late in the period, persistent inflation, more hawkish central bank messaging and a continued regulatory crackdown in China all affected investor sentiment. The health care sector was slightly ahead of the equity market averages amidst a distinct split amongst the three industry groups that comprise the bulk of the fund's portfolio. Biotechnology stocks managed a modest overall gain on the benchmark Nasdaq Biotech Total Return Index, pharmaceutical stocks traded substantially lower despite showing some resilience during September's global equity selloff, while companies in the life sciences tools and services industry posted summer declines that worsened through end-September.
- For the quarter, the fund's A (acc) USD shares returned -5,06%, and its benchmark, the NASDAQ Biotechnology Index, returned -1,22%.

QUARTERLY KEY PERFORMANCE DRIVERS

	Stocks	Industries
HELPED	Trillium Therapeutics (Off-Benchmark Exposure)	Life Sciences Tools and Services (Underweight)
	Ascendis Pharma (Overweight)	Health Care Services (Underweight)
	Adagio Therapeutics (Off-Benchmark Exposure)	—
HURT	Moderna (Significant Underweight)	Biotechnology (Stock Selection, Underweight)
	Heron Therapeutics (Off-Benchmark Exposure)	Pharmaceuticals (Stock Selection, Overweight)
	Jazz Pharmaceuticals (Overweight)	—

- While the majority of the fund's largest biotechnology industry detractors suffered double-digit percentage declines over the July–September span, some the most detrimental impacts on our results versus the index stemmed from the portfolio's performance differential in BioNTech and a deep underweighting in Moderna (at 3.4% of total net assets versus 11.1% of the index's overall composition). We purchased BioNTech shares just ahead of a late summer selloff, resulting in a significant loss, while the stock rose nearly 22% on the index for the full quarter. Meanwhile, Moderna was our top absolute contributor despite the relative weakness. Moderna continued to execute on its COVID-19 vaccine portfolio and was contending with resurgent demand given the highly contagious Delta variant, and the stock, after quadrupling this year (and by roughly tenfold since the start of the pandemic), appeared to be pricing in a considerable amount of recurring revenue and pipeline progress. The shares moved higher as second-quarter earnings came in well above forecast.
- Heron Therapeutics' second-quarter financial results undershot the company's guidance as a modified version of newly approved non-opioid painkiller ZYNRELEF was experiencing clinical trial headwinds with the company seeking to expand beyond ZYNRELEF's currently narrow FDA-approved label. The company believes it can secure a broader label with additional studies, but the narrow label will likely impact ZYNRELEF's growth trajectory. Meanwhile, Jazz Pharmaceuticals shed about a quarter of its equity value, but we still believe it holds strong potential. The company's latest quarterly earnings results came up short on sales of some key products, resulting in a steeper-than-expected overall loss for the April-June period. However, Jazz's newest drugs are contributing to the bottom line while the firm works to unlock more growth opportunities. Jazz has continued to make headway with its long-standing leadership in the sleep medicine market, as well as a wave of new additions to its product line-up including the integration of its recent acquisition of cannabinoid-focused biotech GW Pharma (which helped diversify Jazz's cannabis-derived medicine pipeline into a range of increasingly popular seizure- and spasticity-related therapies).
- Biotechnology industry results were buoyed by rallies in several overweight or off-benchmark holdings, some of which were due to clinical trial successes, better-than-expected quarterly financial results, and/or synergistic acquisitions. In particular, Pfizer (not a fund holding) announced an offer to acquire top contributor Trillium Therapeutics—a developmental-stage, blood cancer-focused biotech company—for US$18.50 per share or US$2.26 billion total, and a 204% premium over Trillium's closing price ahead of the deal. We think it is a good fit for Pfizer, as they get a CD47-focused pipeline (CD47 is an immunoglobulin that is overexpressed on the surface of many types of cancer cells) that is potentially as efficacious as—if not better than—Gilead's magrolimab (Gilead is also owned by the fund), and for less than half of what Gilead paid for Trillium rival Forty Seven in 2020. In some ways the acquisition was not that surprising, given that Pfizer made a US$25 million equity investment in Trillium last year. Trillium's anti-CD47 antibodies are the only ones to have shown monotherapy activity in lymphoma, whereas magrolimab and others are used in combination with other antibodies. Importantly, Trillium's treatments are also better tolerated than magrolimab and other competitors since they do not cause anaemia.

ONE-MONTH KEY PERFORMANCE DRIVERS

	Stocks	Industries
HELPED	Arcus Biosciences (Off-Benchmark Exposure)	Life Sciences Tools and Services (Underweight, Stock Selection)
	Acceleron Pharma (Overweight)	Pharmaceuticals (Overweight)
	BioNTech (Underweight)	—
HURT	Moderna (Significant Underweight)	Biotechnology (Stock Selection)
	Forte Biosciences (Off-Benchmark Exposure)	—
	Apellis Pharmaceuticals (Overweight)	—

- Biotechnology holdings were slightly behind the index in September, yet we held many individual positions that bucked the overall downtrend and rallied solidly. In particular, cancer drug developer Arcus Biosciences has been making progress with one of the most closely-watched clinical trials of 2021—ARC-7, which is the company's Phase 2 trial for domnavalimab (anti-TIGIT antibody) for lung cancer, is on track to report results in the first half of 2022. There has been growing interest in TIGIT as a target for cancer, especially after Arcus's competitor Roche demonstrated additive efficacy when combined with an anti-PD-L1 antibody. Arcus is testing domnavalimab in combination with their own anti PD-1 antibody zimberelimab, as well as in a triple combination of the two plus etrumadenant (A2A/2BR antagonist), and while the company has not reported initial efficacy results yet, Arcus management has noted that the triplet appears to be highly efficacious thus far.
- Middle-capitalisation biotech Acceleron's equity value surged by nearly a third during the month, ahead of Merck announcing an agreement to purchase Acceleron for $180/share or ~$11.5B. Acceleron focuses on therapeutics to treat serious and rare diseases. Its products include Reblozyl, which is already approved for patients with chronic anaemia associated with beta-thalassemia and myelodysplastic syndromes, and sotatercept, which is in late-stage development for pulmonary arterial hypertension.
- Amongst the major detractors, both Forte Biosciences and Apellis Pharmaceuticals announced negative clinical trial results. Forte shed most of its equity value after reporting top-line data from its Phase 2 study evaluating FB-401—the only candidate in its product pipeline, which is intended to treat atopic dermatitis—that showed the drug did not meet the primary endpoint of the study. Apellis, which focuses on rare diseases, sold off as investors reacted to conflicting clinical trial data for the company's experimental blindness prevention drug. Apellis earned FDA approval for its first drug, Empaveli, in May, so there is still a lot riding on pegcetacoplan, the next potential new drug emerging from the company's pipeline. The drug is designed to treat geographic atrophy, an advanced and aggressive form of age-related macular degeneration, or AMD. Apellis still plans to submit a new drug application to the FDA for this drug in the first half of 2022.

Outlook & Strategy

- The past several months have been challenging for biotechnology firms as the industry's overall equity market selloff from February through July represented a sharp reversal from record highs, though the losses were nearly recouped in August and September. As the pace of vaccinations has picked up worldwide, investors have increasingly turned their focus to reopening and an economic rebound, with many rotating out of biotech/pharma and into cyclicals, financials, energy and the COVID-19 recovery trade. Furthermore, a string of high-profile clinical trial failures and regulatory disappointments, as well as a resurgence in drug-pricing policy discussions, continue to weigh on the sector. That said, the recent surge in merger-and-acquisition (M&A) activity in the third quarter has helped improve sentiment somewhat.
- The recent approval by the US Food & Drug Administration (FDA) of Biogen's (held by the fund) Aduhelm—an amyloid beta-directed antibody indicated to treat Alzheimer's disease—has sparked mixed emotions amongst investors, but ultimately, we find the agency's decision to be a net positive for the sector. The FDA is signalling a strong willingness to accept a "mixed" data package for high unmet need indications that have been underserved by existing drug treatments. This flexibility appears justified for a disease like Alzheimer's, but time will tell if the FDA's controversial decision is vindicated. Concerns over pricing and access should abate over time and we see several potential avenues for Medicare to obtain the necessary means to pay for the drug. While a direct readthrough from the Aduhelm decision to other drug programmes is less clear, we believe several neurodegenerative disease areas stand to benefit, including Huntington's Disease, frontotemporal dementia, ALS, and genetic forms of Parkinson's disease.
- Heading into September, our strategy remained unchanged despite the somewhat erratic path of biotechnology equities over the past seven months. As always, we continue to concentrate our investments in biotech companies whose products are best-in-class, first-in-class or only-in-class, and that address diseases with significant unmet medical need delivering clinical value to patients, physicians and payors. Furthermore, we are mindful of valuation, as well as quality of management and financial position in the current environment.
- While the sector has remained relatively resilient throughout the pandemic, we expect a fuller recovery in the coming months as operations that were disrupted by the pandemic continue to return to normal. Some commercial-stage companies struggled with new drug launches during the pandemic, while earlier-stage companies saw some disruption in starting new clinical trials or maintaining the pace of enrolment in existing trials. As vaccinations have enabled a gradual reopening in many parts of the world, clinical development and commercial sales have started to recover. Lastly, most of the developmental-stage companies we invest in rely on capital markets to finance their business models. Fortunately, after a short COVID-19-induced pause, the biotech financing window has been wide open thus far in 2021.
- While the recent discussion on drug pricing reform has renewed investors' concerns this summer, we continue to believe that it will be very difficult to implement any legislation that dramatically alters the current economics of the biopharmaceutical business model. The combination of the new US presidential administration under Joe Biden and the Democrat-controlled US Congress could increase the chance of passing Democrat-sponsored prescription drug price legislation over the next few years. However, drug pricing was not a major policy focus for Biden's campaign or the early phase of his presidency, and drug pricing discussions will likely continue to take a back seat to the pandemic response, in our view.
- M&A activity remains a key driver for the sector. While M&A activity was minimal in the first half of the year, several acquisitions were announced in the third quarter, including Pfizer for Trillium, Sanofi for Kadmon and Translate Bio, and Merck for Acceleron. We are hopeful that this consolidation can continue given the robust stream of innovation flowing from numerous small- and mid-capitalisation biotechnology companies, coupled with weakening product pipelines and strong financial positions at the larger biopharmaceutical companies.
- Over the longer term, we are excited about the tremendous amount of innovation taking place. We are particularly enthusiastic about the recent advancements made in the areas of gene therapy and gene editing, immuno-oncology and precision oncology. We are encouraged by novel mechanisms to address diseases with high unmet medical need, including Alzheimer's disease, other neurodegenerative disorders, and autoimmune diseases. We also see opportunities at the other end of the "prevalence spectrum" in addressing rare diseases. We are further encouraged by what we are seeing in background processes, as many novel discovery tools are being used behind the scenes to enable faster drug discovery and development.

Fund Details

Inception Date	03/04/2000
Benchmark	NASDAQ Biotechnology Index

Fund Description

The fund aims to achieve capital appreciation by investing principally in equity securities of biotechnology companies and discovery research firms located mainly in the US.

Performance Data

Discrete Annual Performance (%) as at 30/09/2021

	9/20-9/21	9/19-9/20	9/18-9/19	9/17-9/18	9/16-9/17
A (acc) USD	0,17	46,47	-18,08	1,28	16,23
NASDAQ Biotechnology Index USD	19,46	36,10	-18,45	9,80	15,39

Performance Net of Management Fees as at 30/09/2021 (Dividends Reinvested) (%)[a,b]

	1 Mth	3 Mths	YTD	1 Yr	3 Yrs	5 Yrs	10 Yrs	Since Inception (03/04/2000)
A (acc) USD	-4,68	-5,06	-9,31	0,17	6,32	7,19	15,19	6,77
NASDAQ Biotechnology Index	-4,91	-1,22	6,85	19,46	9,85	10,93	18,11	7,54

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