Investable innovation: Tracking remarkable biopharmaceutical advances

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UOB Asset Management

Opportunities in health care abound and we believe the long-term outlook for the sector is positive, powered by demographic trends, a record-setting pace of innovation, and structural changes in health care delivery systems. The pace of drug discovery is at an all-time high, new tools and modalities are enabling scientists to develop innovative treatments for diseases with major unmet needs. These continue to drive growth in the sector and expand the investment universe.

We explore the key to biotechnology investing, outline drivers of the sector and delve into new paradigms and modalities of treatment. We also take a look at various frontiers of drug discovery, the risks involved and the investment opportunities. Emerging markets also potentially offer rich pickings for health care investors. A fast-growing market centred in Asia features innovative companies serving large local markets and competing on a global scale.

Getting to the crux of Biotechnology investing

As with all forms of investing, we believe the key to investing in biotechnology is to understand the inefficiencies of the market and to exploit them with one's skills and experience. In biotech, the principal inefficiency stems from the opacity of scientific data, and the resultant inability of market participants to agree on the merits of a given drug development programme. This causes substantial volatility in valuations — independent of scientific progress or lack thereof — potentially enabling patient and discerning investors to build investment positions before the true value of a drug development programme is reflected in a stock's price.

In our view, the key is to try to identify — ahead of the market, and based on rigorous scientific evaluation — which programmes are likely to yield important new drugs, and which are not. The repeated ability to do this increases the probability that one can profit in the sector while also mitigating risk. The team that covers the healthcare sector draws upon its diverse academic, scientific, and clinical backgrounds, which include professional careers in science and medicine, to make their investment decisions. The combination of scientific fluency, business acumen, and long investment experience enables us to analyse drug development programmes thoroughly and holistically, both at the company and industry level.

In evaluating investment opportunities, we aim to consider all relevant factors, including basic scientific mechanisms of disease, reasons why toxicity may emerge, the best biochemical nodes at which to intervene, the chemical and biochemical properties of drug candidates, and their preclinical and clinical profiles. We also deliberate non-scientific factors, such as ease of manufacturing, intellectual property protection, commercial market dynamics, and payer mix. Our goal is to reach accurate conclusions about the value of drug programmes and the companies that develop them.

Drivers of biotechnology

The world has benefitted from amazing advances in biotechnology. The industry is now being driven by incredible new tools that are enabling scientists to understand human biology at a much more profound level than ever before, greatly improving comprehension of the specific causes of disease and allowing them to identify molecules to treat them. Prior to about 1975, drugs were developed by screening animal models of disease — a slow, cumbersome, and moderately informative approach. The 1980s saw a big leap forward, as modern biochemical analyses that revealed results faster and more accurately replaced much of the animal work. This led to a raft of new drugs for major indications, including high blood pressure, high cholesterol, and depression — biochemical targets that are relatively easy to address. During that decade, the industry began to use proteins as therapeutic agents, building on advances in cloning and molecular genetics that had originated 20 years earlier.

Progress continued in the 1990s, as monoclonal antibodies entered the therapeutic tool kit. But momentum slowed somewhat thereafter, as very specific scientific advances were needed to crack the next layer of difficulty. By the early 2000s, the full DNA sequence of the human genome was in hand, as were new tools in microfluidics, bioinformatics, subcellular pathway analysis, and genetic manipulation. In addition, fundamental discoveries about the pathophysiology of certain diseases allowed drug developers to tackle a whole new set of drug targets that were much more complicated and elusive than those targeted in the 1980s. Since then, entirely new treatment paradigms have been developed, setting the stage for where we are today. In the coming decade, we should witness the arrival of a host of wonderful new drugs and novel treatment modalities.

New modalities of treatment

Among the most exciting and investable new modalities of treatment are: 1) gene therapy, 2) gene editing, and 3) cellular therapy.

Gene therapy delivers genetic instructions into a patient's cells to reverse the harmful effects of a missing or defective gene. This technology is already being used to treat several lifelong crippling diseases. With hemophilia, for example, deficient blood clotting can

lead to catastrophic bleeding, with attendant tissue and organ damage and a degraded quality of life. Hemophilia occurs in patients born without the gene that directs production of a certain blood-clotting factor. Traditional treatments involve frequent infusions of a replacement factor, a cumbersome and expensive method that is only partially effective and exposes the patient to the risk of infection. In contrast, gene therapy may be a one-time treatment that induces the body to produce enough of the missing factor on an ongoing basis to correct the bleeding problem and allow hemophiliacs to lead normal lives. The approach is being studied in other blood diseases such as sickle cell anemia and thalassemia, and it has proven effective in treating certain retinal diseases. Gene therapy is currently limited in its ability to target only diseases of tissues or organs that are easily accessible to the intervention, including the eyes, blood, and liver. There are other challenges, which several companies are actively seeking to overcome.

Gene editing, using the CRISPR system, is a new technology that can make extremely precise changes in a patient's genetic material. CRISPR (clustered regularly interspaced short palindromic repeats), builds on the astonishing discovery of a bacterial defence system that protects the bacteria from viruses, which has been adapted for genome editing. Because it is more flexible and potentially less disruptive than gene therapy, CRISPR introduces the possibility of correcting an inborn genetic error regardless of type, as opposed to replacing a defective gene in parallel. It can be used to either completely replace a missing gene or to deactivate a harmful gene that is causing disease. Because of this, it has potentially broader applications than gene therapy. Clinical use of CRISPR is in its infancy but could advance rapidly.

Cellular therapy is being studied as a cancer treatment. Healthy, living cells that normally function to protect the body from infectious agents or tumours are harvested from the patient or a healthy blood donor, and reengineered by changing their genetic code to turn them into cancer fighting machines. To date, this strategy has been most productively applied with T-cells, one of the primary cells of the body's immune system. Engineered chimeric antigen receptor T-cells, or "CAR-Ts", have produced amazing clinical results, particularly in children with late-stage leukaemia, for whom other hopes for a cure have been exhausted. CAR-Ts have also been shown to be active in the treatment of lymphoma. The first CAR-T therapy was approved by the US Food and Drug Administration in 2017.

Investment opportunities for new treatment modalities

In terms of the investment opportunity set for these new treatment modalities, there are several dozen publicly-listed biotechnology companies that specialise in the development of gene therapy, gene editing, and cellular therapy approaches for the treatment of human diseases. Many are small- or mid-cap companies under US$5 billion in market capitalisation, and this number is growing every year. In addition, more traditional biopharmaceutical companies are adopting these new modalities in their pipelines.

Risks of genetic engineering

The biggest risk of genetic engineering, regardless of approach, is the inadvertent creation of harmful mutations in the target DNA. This could occur in a number of ways, and could potentially cause abnormal cellular growth, leading to cancer. Cancer is a theoretical risk here, but not a trivial one; when one alters the blueprint of life, one may unintentionally introduce problematic changes to the genome.

Developments in immuno-oncology

Another treatment modality is immuno-oncology (IO), which is still in very early stages of growth. With IO, drugs are given to enable a patient's immune system to fight cancer, either by removing obstacles or optimising immune actions. The goal is for the body to recognise cancer cells as foreign and produce quality "fighter cells" in optimal proportion. These fighter cells then travel to the right location with sufficient power to eliminate the cancer and prevent recurrence. Immuno-oncology accounts for more than 50 per cent of spending in the biopharmaceutical industry, and new discoveries are happening all the time. The science is enabling IO to be used far more broadly than the market realises. We believe the investment opportunity set is upwards of US$60 billion. Several market inefficiencies provide investment opportunities in IO. For example, while most IO successes to date have been in late-stage cancer, we expect the most significant uses going forward to be in the earlier-stage treatment population, which is much larger. So far, the investment community has not fully embraced the breadth of the IO opportunity in early-line treatment and assigns little value as yet to the IO opportunity in most pre-metastatic cancers. But IO responses have already translated into higher survival rates than traditional chemotherapy, with multiple trials corroborating early progression metrics. Overall, the durability and depth of response for IO should be even better in earlier disease stages, when patients have stronger baseline health and relatively uncompromised immune systems.

The power of combinations — stacking several IO treatment agents with different mechanisms — is another opportunity driver that has the potential to increase the number of patients who respond. IO uses are proliferating, including approaches that apply IO to treat hundreds of types of cancer. Today, many of these are in human trials using first- and subsequent-generation IO agents. There is rapid progress in predictive techniques to determine where IO agents may be most effective. And finally, the structures for delivering immune therapies are improving, potentially leading to more effective treatment outcomes.

In this growing investable universe, we believe the key is to identify potential "winners" and "losers." Cancer is a highly heterogeneous disease; each tumour type likely has many different recipes for treatment. Successful companies are studying their oncology portfolios with an eye on multiple strategies for each different tumour, quickly learning to identify markers that predict which patients will respond to treatment. This knowledge will likely lead to even better mapping of patients to these different therapies. We believe that, ultimately, a broad arsenal of mechanisms will prove the best strategy, so owning the rights to a range of IO and complementary mechanisms should afford good companies more flexibility on their clinical-trial strategy and pricing upon approval.

Other intriguing areas of drug development

There are many other areas of drug development that are intriguing, and here we discuss two. The first area is a class of underappreciated oncology drugs that we term "smart chemos". Used alone, these agents do not have much effect on a tumour, nor do they make a patient sick the way traditional chemotherapy does. When carefully paired with another agent, however, the two-drug combination produces remarkable anti-tumour activity with little additional toxicity. This is akin to two beams of light focused on a single point.

An example of smart chemos is the group of drugs used to target the poly(ADP-ribose) polymerase (PARP) family of proteins involved in cellular processes like DNA repair and programmed cell death. These have shown phenomenal activity in ovarian cancer when given immediately after a course of conventional DNA-damaging chemotherapy. Another example is cyclin-dependent kinase (CDK) 4/6 inhibitors, which have had great efficacy in the treatment of breast cancer when combined with an anti-hormonal agent. These smart chemos may well have far greater clinical use than what is priced into stocks today. There is no reason to believe, for example, that PARP inhibitors will only be useful in ovarian cancer, or that they can only be paired with certain chemotherapeutic agents. In fact, they will more likely be broadly useful as long as amenable patients can be identified in advance. We believe that biopharmaceutical companies developing these treatments are not being given credit for their potential.

A second fascinating area is neurology. Tremendous progress in the basic understanding of neuroscience is widening the opportunity set in neurology drug development. Encouraging new treatments for everything from headaches to depression to neurodegenerative conditions like Alzheimer's disease are being developed. A new class of agents called CGRP (calcitonin gene-related peptide) antagonists that have shown impressive benefits in treating migraines entered the market in 2018, for example. Progress is ongoing; while the first generation of CGRP antagonists is effective, patients must undergo regular intravenous infusions. We believe that a second generation of CGRP antagonists, which can be taken orally, presents an even greater opportunity. These agents have successfully concluded a number of late-stage clinical trials and are expected to be approved in 2019.

Several companies in our coverage universe are in late-stage trials with promising new drugs to combat forms of depression that have thus far been resistant to almost anything doctors have prescribed. And finally, advances in the treatment of Alzheimer's disease remain an enormous opportunity set, with current data suggesting that meaningful disease-modifying therapies are only a few years away. Because the nervous system is the most complex system in the body, neuroscience arguably stands to benefit most from increased scientific understanding of disease mechanisms and pathways.

Emerging markets as an important part of global health care coverage

Shifting gears to the global health care arena, we see demand growing fast in emerging markets. Aging populations, increased personal wealth, government health care reform, and a rise in chronic disease are all contributing to increased spending on health care. In many developing countries, health care spending has grown significantly faster than the overall economy for many years. Governments increasingly need to turn to the private sector to help build a more robust health care infrastructure. In addition, developing a strong local biopharmaceutical industry becomes a strategic priority over time, reducing a developing country's dependence on imported medicines and showcasing its research and innovation capabilities.

The rise of innovation in certain emerging markets is a very recent development that presents new investment opportunities. In China, biomedical innovation is flourishing thanks to increased investment, an influx of skilled labour, and loosened government regulations. A 2008 government initiative called the Thousand Talents Programme encouraged many Chinese-born, US-trained scientists to return to China, with the promise of research funding and tax incentives.

In terms of regulations, reforms at the China Food and Drug Administration have helped streamline the drug approval process and level the playing field for local and multinational companies. Anti-corruption measures are beginning to help as well. In addition, modifications to the drug pricing and reimbursement system are positive for the industry's long-term growth. Increasingly, novel drugs will be priced for the value they deliver, while older, off-patent drugs will face stiffer price cuts and increased competition. We think this creates attractive incentives for companies investing in innovation.

Another notable area of interest is biosimilars. Biosimilars are cheaper generic copies of complex injectable drugs called biologics. Making biosimilars is a capital-intensive process, and successful clinical development requires scientific and regulatory skill. A few companies in emerging markets have the ability to compete effectively here, and they enjoy cost advantages not always shared by

counterparts in developed markets. Two South Korean companies sell biosimilars into developed markets today, for example. In addition, pharmaceutical companies in China, India, and Eastern Europe have developed biosimilars for their local markets, helping to broaden access to many highly effective therapies.

In conclusion, despite recent volatilities, we believe opportunities in the health care sector remain abundant. Powerful demographic trends, a record-setting pace of innovation and drug development, and structural changes in health care delivery systems continue to drive growth and expand the investment opportunity set in an industry that has a positive structural outlook.

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