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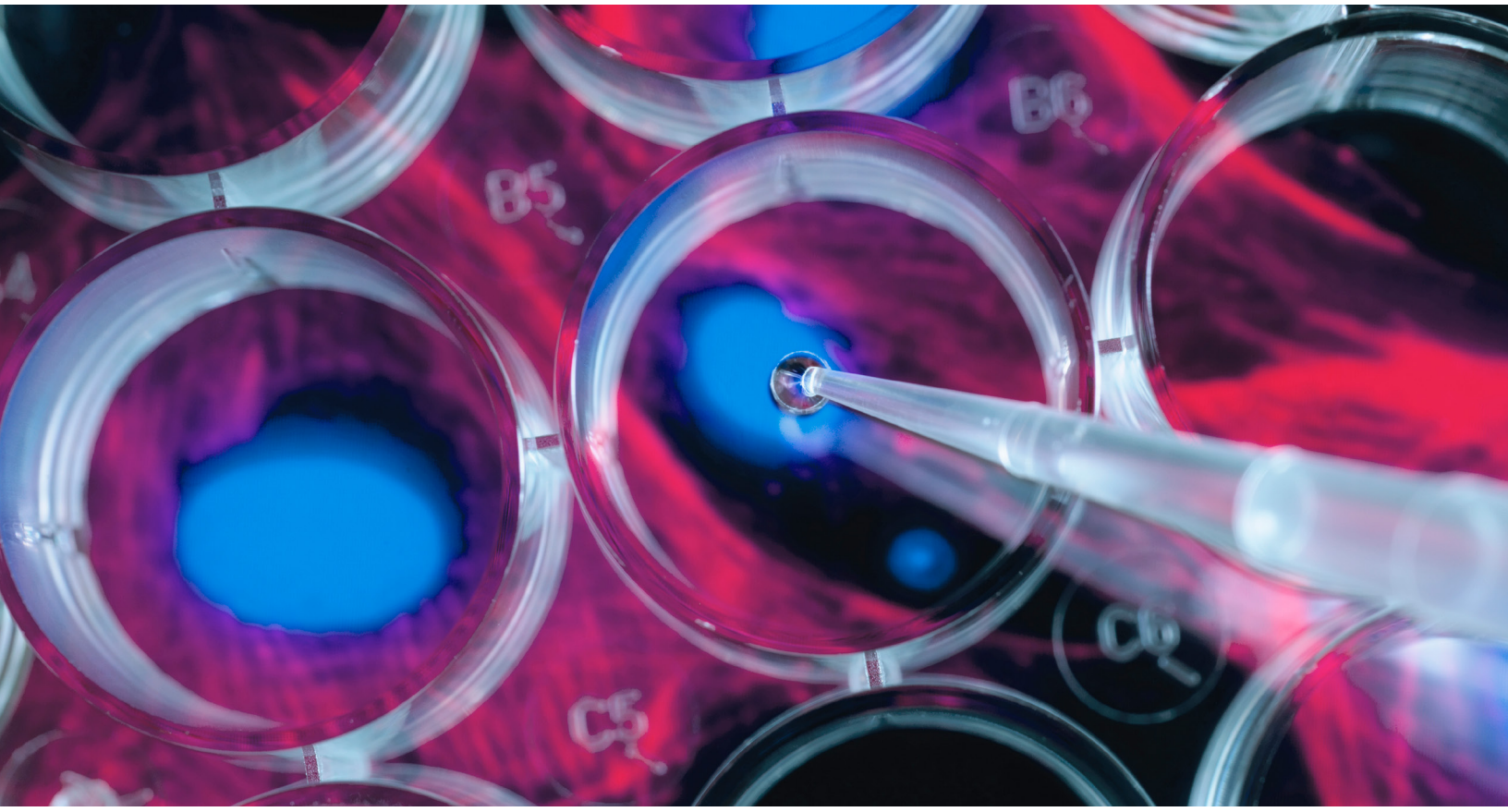
Biopharma portfolio strategy in the era of cell and gene therapy

Many biopharma companies are investing in cell and gene therapy, albeit cautiously, amid a nascent market. Understanding investment opportunities and entry strategies will help guide their portfolio decisions.

by Toby AuWerter, Jeff Smith, and Lydia The



April 2020

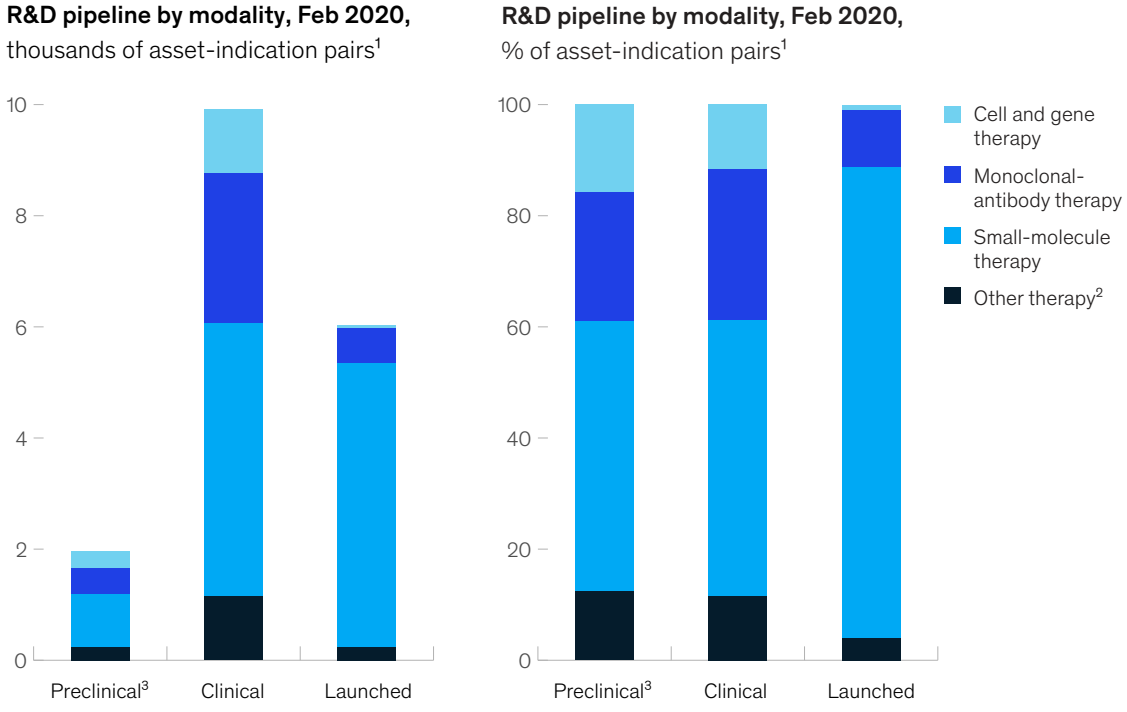
The potential importance of cell and gene therapy (CGT) to healthcare and the biopharma industry seems clear.[1] CGT accounts for just 1 percent of launched products in major markets, with treatment of the vast majority of diseases still using small-molecule drugs. Yet those products—which include cell therapies, such as chimeric antigen receptor (CAR) T-cell therapy for aggressive B-cell lymphomas, and gene therapies to treat a range of monogenic rare diseases—have proved transformative for patients. And there are many more in development. As of February 2020, CGT products account for 12 percent of the industry's clinical pipeline and at least 16 percent of the preclinical pipeline, but as most manufacturers do not disclose their preclinical assets, the true figure may be considerably higher (Exhibit 1).

New CGT products will surely emerge from this pipeline upon the continuing discovery of indications that CGT can address and the growing industry understanding of the genetic drivers and determinants of more complex, multifactorial diseases. Indeed, the pace of CGT-asset development is similar to that of monoclonal-antibody (mAb) assets in that modality's early years, and mAb therapy went on to transform the biopharma market (see sidebar, "Cell and gene therapy: Mirroring monoclonal-antibody therapy").

Exciting clinical results are helping to propel this pace. Success rates for CGT products are higher than those for small-molecule products, probably because CGT tends to target specific disease drivers rather than the broad targets (with potential

Exhibit 1

R&D pipelines suggest high hopes for cell and gene therapy.



[1]Asset-indication pair: 1 trial per asset indication (eg, trial of KYMRIAH for refractory B-cell acute lymphocytic leukemia).
[2]Includes vaccines, proteins, and peptides.
[3]Underestimation of preclinical pipeline, as most manufacturers don't disclose preclinical assets.

Source: Pharmaprojects, Informa, pharmaintelligence.informa.com

[1] For this article, we define cell therapy as the therapeutic use of human cellular material with biological activities that cause a desired effect in vivo. We define gene therapy as the direct, in vivo administration of DNA-based therapy (most commonly delivered using a viral vector, such as a lentivirus or adeno-associated virus).

for off-target effects) of small-molecule therapy. The sample size of launched CGTs is small, so comparisons may change as the market evolves. Nevertheless, there is a marked difference thus far. Between 2008 and 2018, the R&D success rate from Phase I to launch for small-molecule products was 8.2 percent; for CGT products, it was 11 percent.[2]

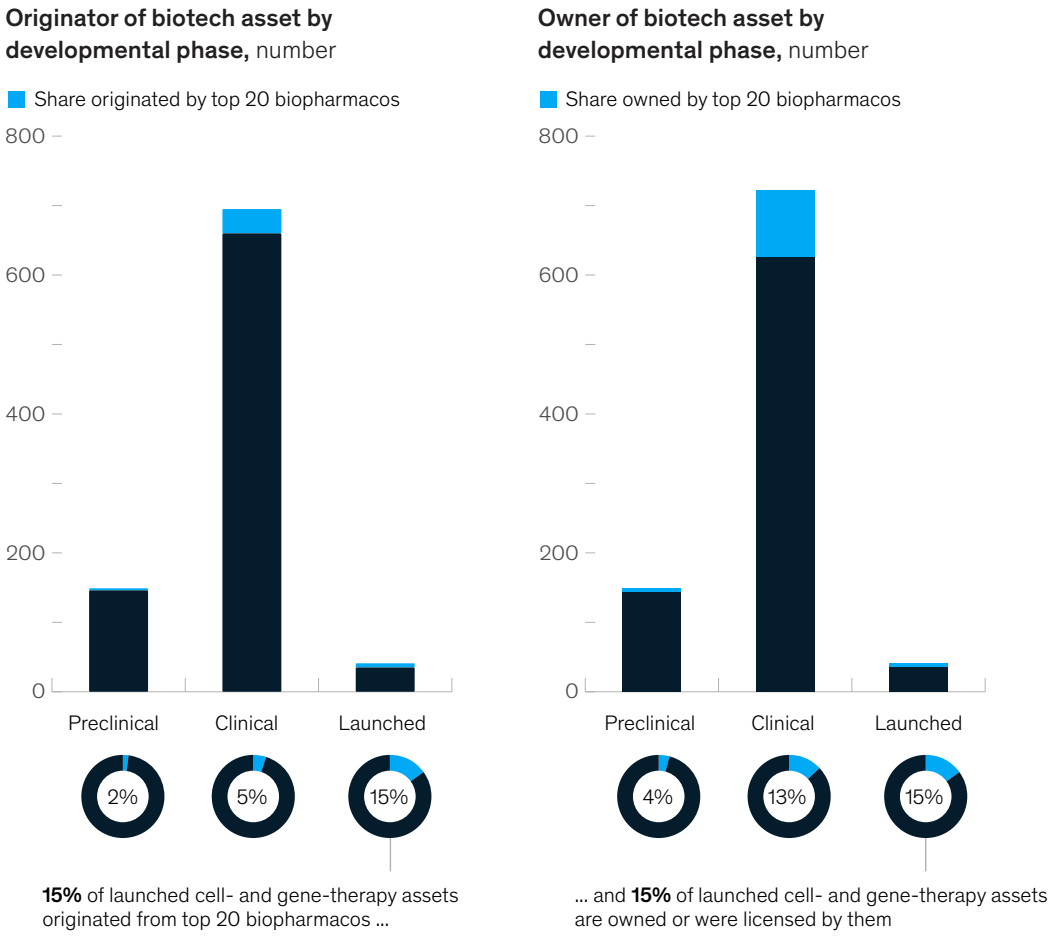
Recognizing CGT's potential, 16 of the world's largest (by revenue) 20 biopharmacos now have CGT assets in their product portfolios. Yet most companies are moving cautiously—only two of the top 20 have CGT assets making up more than 20 percent of their pipelines. They are still considering whether, when, and how to reposition their portfolios. In the meantime, biotech companies remain leaders in CGT innovation.

As of February 2020, only a small percentage of launched CGT assets either originated from or are owned by a top 20 biopharmaco—in both cases, only 15 percent of launched assets—indicating how much opportunity there is for such companies to increase their exposure to CGT assets (Exhibit 2).

The figures are not altogether surprising, given that biopharmacos' expertise often lies in disease

Exhibit 2

Biotech companies lead innovation in cell and gene therapy.



Source: Pharmaprojects, Informa, pharmaintelligence.informa.com

[2] Pharmaprojects, Informa, December 2019, pharmaintelligence.informa.com; McKinsey analysis.

Given CGT's growth potential and the promise it holds for patients, most large biopharmacos are considering increasing their market presence.

areas, not in the development of the technology platforms that generate CGT products. More often than not, the original research behind new platforms is conducted by academics (who go on to set up their own biotech companies) and investors (whose models include company origination because of the potential financial gains and the concentrated technical risk that platform investments carry). Venture-capital firms are more comfortable than established biopharmacos with such risks.

Nevertheless, given the growth potential of CGT and the promise it holds for patients, most large biopharmacos are considering increasing their presence in the market. This article is intended to help guide their decisions, describing the key considerations when assessing investment opportunities and the various entry strategies—as well as the trade-offs to be made when choosing among them.

Assessing investment opportunities

There are many technology platforms in development that seek to address different challenges associated with CGT. In cell therapy, work is afoot to improve the manufacture of autologous therapies to reduce the cost of goods sold or vein-to-vein time, enable breakthrough efficacy in solid tumors, and improve the patient or customer experience. In gene therapy, there are investment opportunities in platforms that aim to overcome the limitations of current vectors (such as the size of the transgene, suboptimal tropism, or the triggering of an immune response) that enable nonviral delivery methods, reduce manufacturing costs, and expand manufacturing capacity.

The decision, therefore, is about not only whether to increase investment in CGT but also which technology platforms or assets to back. Companies should thus assess each investment opportunity by both strategic fit and technology attractiveness. Strategic considerations on a CGT platform or asset include whether it complements a company's disease areas of focus, the internal pipeline would benefit from diversification with new modalities, and the company has the required capabilities, capital, and conviction.

A host of questions need to be asked to gauge the attractiveness of the technology. Has it demonstrated proof of concept? What risks remain? Does the company have enough understanding of the underlying mechanisms? Does the technology enable first-mover advantage? What are the intellectual-property considerations? Is the platform differentiated from competing platforms? And given the rapid pace of innovation in CGT, what is the risk that the technology platform quickly becomes obsolete?

CAR T-cell therapy, whereby a patient's T cells are genetically engineered to express a chimeric antigen receptor that targets a specific tumor antigen, illustrates the potential risk. In a relatively short time, the field has progressed from an initial set of constructs to a second generation that has given rise to two FDA-approved products, YESCARTA and KYMRIAH, even as third- and fourth-generation products are in development.

Investment opportunities that have a strong strategic fit and high-potential technology—those that fall into the top-right quadrant shown in Exhibit 3—will be attractive. For example, a CAR T-cell or

T-cell-receptor platform would fall in the top right for many oncology-focused companies. In the absence of such opportunities, those in the top-left or bottom-right quadrants may still be worthwhile as a means of gaining exposure to CGT, perhaps through an early-stage investment. For example, next-generation, unproven gene-editing technologies may fall in the bottom-right quadrant for companies focused on rare diseases with known genetic drivers. Companies would have to be prepared to tolerate the associated risks, however, and not all will conclude that now is the time to make a move.

Assessing entry strategies: Homegrown, bought, or partner developed?

Once a manufacturer has decided that it makes strategic sense to invest in CGT and has identified an attractive technology, it must choose an entry strategy. There are three main options: build a proprietary platform, buy an existing platform or one or more of its assets, or form a partnership to gain access to assets on platforms developed by others (Exhibit 4). The three options have different profiles in the capital required, changes to the operational model needed, and risk (as measured by the degree of diversification offered across different technologies).

Companies that build a platform or platforms from scratch enjoy full control over development efforts and retain all the financial rewards of successful assets. They also get the chance to build their own CGT capabilities—scientific, clinical, and commercial—and have the freedom to adapt as the technology evolves. In return, they have to commit significant resources to internal R&D and will, in effect, be placing big, early bets on a single or very limited number of platforms. Additionally, they may need to make significant changes to operating models designed for traditional modalities.

Buying a developed platform or late-stage asset carries less technical risk (assuming robust early data), though invariably a price premium too. This means that few, if any, companies will be able to acquire a large number of them, so companies continue to bet on a single or limited number of platforms.

Exhibit 3

Companies should assess each investment opportunity by strategic fit and technology attractiveness.

How to assess cell- and gene-therapy-investment opportunities

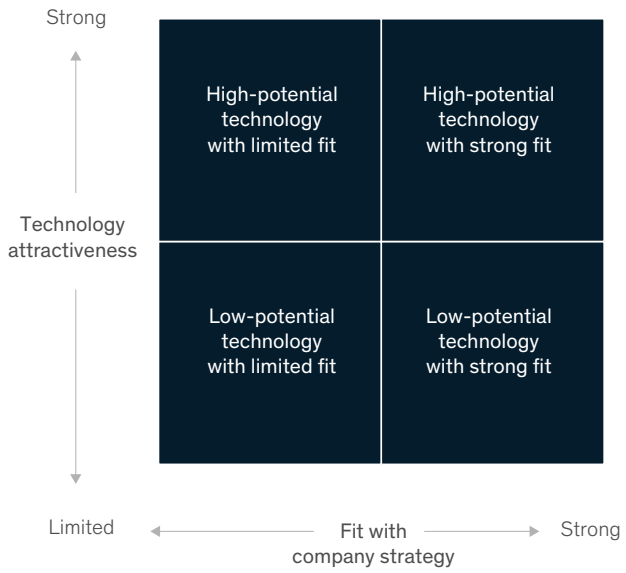
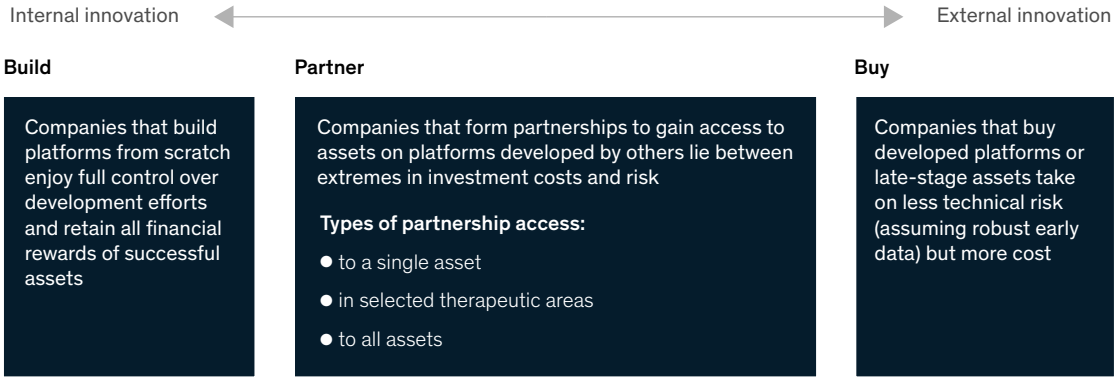


Exhibit 4

Once a manufacturer has decided to invest in cell and gene therapy and has identified an attractive technology, it must choose an entry strategy.

Options for entering cell- and gene-therapy investment



The third option—forming a partnership to gain access to assets on platforms that others have developed—lies between these two extremes in investment cost and risk. Because partnerships in the still-nascent CGT sector are relatively cheap, biopharmacos can afford to spread their bets on where future success might lie through establishing several partnerships.

Accordingly, most biopharmacos to date have followed the partnership route when placing a stake in CGT. Between 2010 and 2014, there were a total of 16 M&A deals in the CGT space. That rose to more than 60 between 2015 and 2019. However, even in 2019, when M&A activity was strongest, partnerships accounted for more than 80 percent of total transaction activity (Exhibit 5). Nearly all the top 20 biopharmacos have formed at least one partnership, while ten have made an acquisition. Just one has built its own platform. Exhibit 6 details this, along with the impact that the deals have had on the composition of company pipelines.

Looking closer at partnerships

Partnerships come in three main varieties: those that give a biopharmaco access to a single asset, those that give it access to all assets in selected therapeutic areas that might emerge from a platform, and those that give it access to all platform assets, regardless of the therapeutic area or indication.

Cell and gene therapy: Mirroring monoclonal-antibody therapy

Therapy using monoclonal antibodies (mAbs), a new modality two decades ago, transformed the biopharma industry. Early signs are that cell and gene therapy (CGT) could have the same impact.

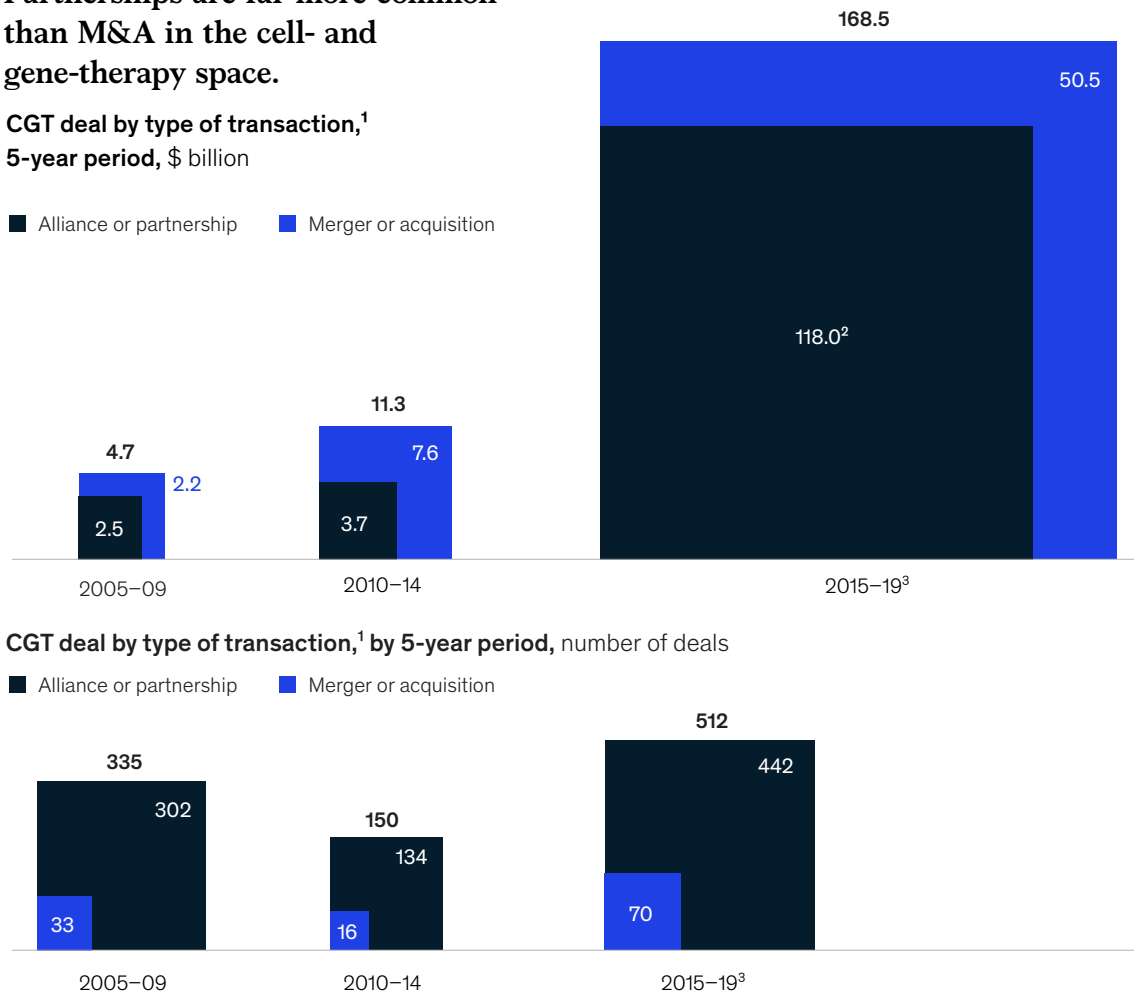
Five years after the 1997 approval of the first chimeric mAb, Rituxan, more than 15 mAb assets were on the market, with yearly sales worth $5.1 billion.[1] By 2018, as more efficient manufacturing methods evolved to improve yields and reduce costs, there were almost 100 mAb products earning annual revenues of $122.5 billion.

The first CGT product reached the market approximately 20 years after the first mAb, but sales projections for the first several years of these two modalities appear to be similar: between ten and 20 assets and annual sales of about $5 billion. If the biopharma industry has even a fraction of the success in developing CGT assets and improving manufacturing methods that it did with mAbs, then it is at the start of what looks set to be an exciting journey.

[1] EvaluatePharma, Evaluate, September 2019, info.evaluate.com.

Exhibit 5

Partnerships are far more common than M&A in the cell- and gene-therapy space.



[1] Excludes manufacturing/supply deals, contract research deals, and grant funding.
[2] Excludes Bristol Myers Squibb and Celgene merger.
[3] As of Sept 2019.

Source: IQVIA Pharma Deals, IQVIA, pharmadeals.net

Partnerships structured to give a biopharmaco access to a single asset are the simplest way to enter the CGT market and are often chosen by companies that have a strong focus on certain indications and believe that their competitive advantage lies in owning multiple therapies across modalities in that space. A single-asset partnership also minimizes the investment required. However, this kind of partnership may leave a biopharmaco having to introduce a new operating model for a single asset.

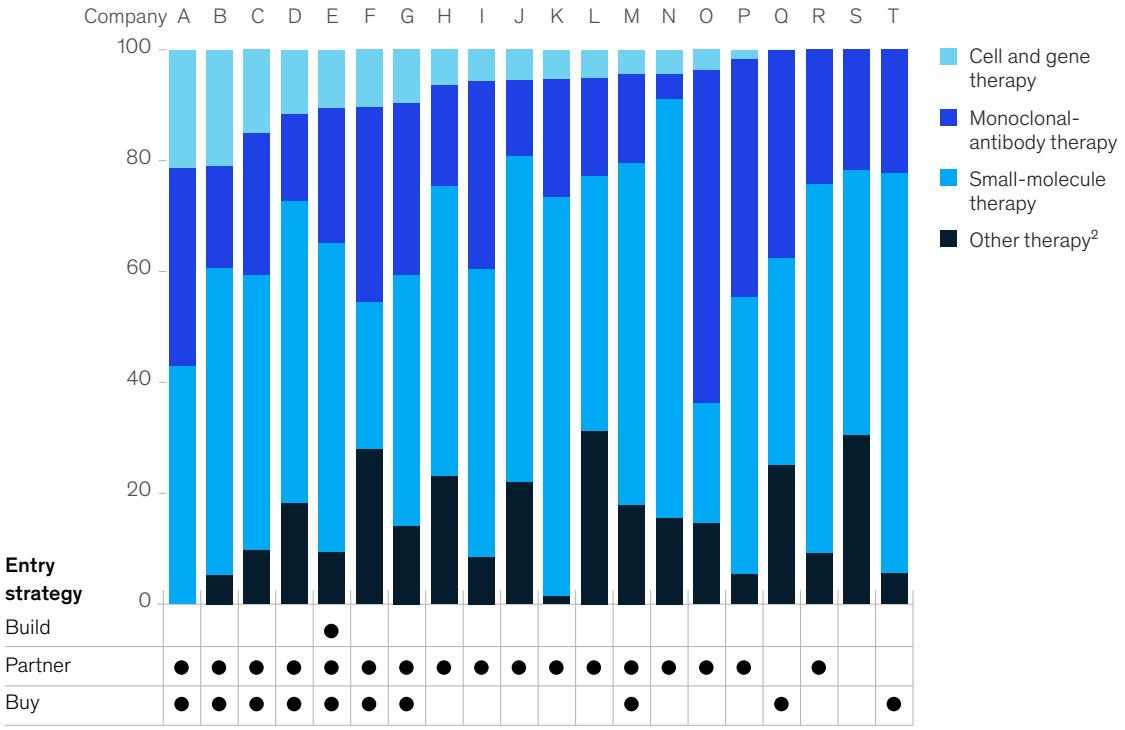
Partnerships structured to give a biopharmaco access to all assets from a platform in certain therapeutic areas can help companies with a strong strategic focus on a given therapeutic area strengthen their portfolios and build more expertise in that area. In addition, more assets in a new modality means more opportunity to build the relevant development and commercial expertise.

The third option, partnering to win access to all the assets in a particular modality generated by a platform, tends to be the partnership of choice for biopharmacos that believe future competitive advantage lies in access to the best technology, no matter what may be the associated indication or therapeutic area. Through such a partnership, a company can "follow the science," developing the technology for the indications in which it can provide the most clinical benefit. Such a strategy requires more investment than other forms of partnership, however, and so carries more concentrated technology risk. Companies may also find themselves developing products for

Exhibit 6

Monoclonal antibodies transformed the biopharmaceutical industry, and cell and gene therapy could do the same.

Pipeline composition for top 20 biopharmacos by modality of asset,[1] % of pipeline



[1]Companies ordered from highest to lowest cell- and gene-therapy pipeline share.
[2]Recombinants, protein extracts, vaccines, chiral chemistry, plant extracts, in vivo diagnostics, and other biotech products.
Source: EvaluatePharma, Evaluate, info.evaluate.com; IQVIA Pharma Deals, IQVIA, pharmadeals.net

therapeutic areas in which they have no expertise and thus are at a competitive disadvantage.

In addition to these three kinds of partnerships with biotech companies, some biopharmacos are considering more innovative ways to allocate their limited resources across multiple CGT technologies in a manner that also boosts their chances of keeping pace with rapid innovation. By partnering with venture-capital firms or biotech originators to launch new assets, new platforms, or even new companies or by collaborating with large academic institutions to license multiple new technologies, they are making much earlier-stage bets on where future success might lie.

The CGT era is an exciting one for healthcare, and all biopharmacos will want to reassess their portfolio strategies to decide whether and to what extent to diversify their pipelines. Most big biopharmacos have chosen partnerships to explore CGT initially, though the likelihood is that many will use a combination of strategies to increase their exposure and access to several technologies as the market evolves. Yet whether a company is still testing the water or is ready to commit, it will need to think carefully about how it builds its exposure to the CGT market and be fully aware of how to assess each investment opportunity, the range of possible entry strategies, and the different advantages and risks that each carries.

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