Rapid Evolution of the Biotech Industry: 2023 and Beyond

The Fast Pace of Biotech

The biopharmaceutical industry has embraced the adage of "Don't be afraid of change, welcome it." In doing so, the industry has fuelled a staggering transformation over the past 20 years. Extremely complex nucleic acid molecules and recombinant proteins with highly defined and functionally sensitive characteristics have been scaled to thousands of litters in commercial-scale bioreactors. The emergence and commercialisation of "living medicines" have allowed reprogramming patient's T cells *ex vivo* to exhibit drastic tumour regression and long-term tumour surveillance, developed gene therapies to reverse monogenic diseases that otherwise have little or no treatment options, and fast-tracked RNA-based vaccines at a scale never attempted to overcome a global health crisis.

Accompanying this exponential growth in developing novel therapeutic modalities, there appears to be a dramatic shift in the underlying occupational market structure. In the past, graduate students who successfully defended their Ph.D. thesis were expected to enroll for additional training as a post-doctoral researcher that would eventually catapult their career to a tenured position within a prestigious university or see them placed in a commercial organisation. However, it now appears that both the National Institutes of Health (NIH) as well as other exclusive academic institutes are struggling to recruit and retain post-doctoral researchers. From 1990–1999, the number of postdoctoral appointees holding non-faculty research positions in science grew 29.8% and likewise, from 2000–2009 grew 27.7%.[1] The following decade, 2010–2019, this metric shrank to a growth of only 3%.[1] Even more alarming, a 4.1% reduction in postdocs was seen from 2020–2021.[1]

Similarly, trends in funding may also indicate a shift in the overall behaviour of the biopharmaceutical ecosystem. Large, more traditional multi-year grants such as the R01 and R21 are ideally suited for academic research, and over the years have served their purpose well. However, more novel mechanisms of funding research, specifically for the development of commercial technologies, have emerged and the frequency of these translational funding mechanisms has surged dramatically.

In fact, a recent study found that programs that include the Small Business Innovation Research (SBIR) and the Small Business Technology Transfer (STTR) programs have provided small businesses with what amounts to 60–65% of the overall U.S. seed funding.[2] Other translational private funding mechanisms, such as angel investors and venture capital (VC), have also surged in popularity over the past decade. In 2016, VCs invested in 2,200 biotech startups globally.[3] In 2021, the number of VC–funded biotech companies jumped 40%, with an estimated raised capital of more than $34 billion globally.[3]

The role of large biopharmaceutical companies has shifted along with these changing times as well. Even with considerable fiscal budgets to spend, large pharma is not leading the pack in this massive push of innovative drug development. In the case of Pfizer, 34 products developed by third parties accounted for 86% of their revenue generated in 2019.[4] Likewise, at Johnson & Johnson, 16 of their 18 portfolio products were not internally developed, which accounted for 89% of their $31.4 billion revenue.[4] So, who is leading the pack in developing all these innovative, revenue generating drugs?

The answer to these three seismic shifts in the biotech industry is emerging tech companies, which are companies with less than $200 million in annual R&D expenditures, and annual sales less than $500 million. These companies were responsible for 67% of approved drugs in 2022.[5] This figure is up by 4% compared to the prior year, and up 33% from a decade earlier.[5] All in all, this staggering innovation push from biotech companies has been steadily increasing year over year at a rate of 4% and is expected to rise as high as 80% within the next five years.[5]

The Innovators

This rapidly evolving landscape is ultimately shifting the identity of the movers and shakers of the industry. Fuelled by these changes in funding mechanisms and uninhibited access to freshly graduated doctorate-level talent motivated by perks not heard of in academia, small biotechs cumulatively form the innovation engine that is driving this drastic global market transformation in the biopharmaceuticals industry. These emerging biotech companies share a somewhat common lifecycle and the desire to pursue exit strategies that are advantageous to them, big pharma, as well as the public.

Small biotech companies commonly spin out of universities or are created through licensing of a significantly enabling technology from a university or research centre.[6] At this stage, many are funded by more traditional grant mechanisms or pre-seed VC investment. Their focus is on conducting significant preclinical research and development work to define their agent's mechanism of action *in vitro* with the goal of conducting subsequent *in vivo* studies in animal models to test specific target disease applications.

A few years into this stage, where their technology is still under development and traditional grant resources have typically been exhausted, companies require additional investment to fill the financial gap and provide runway to move their technology forward. Emerging biotech may receive additional SBIR/STTR funds but are increasingly likely to seek angel, pre-seed, or seed round VC investments because these funding mechanisms can be more substantial, timelier, and often come with business advisement as well as liquid funds. As a measure of how prevalent this is, $21.0 billion in angel and seed funds were invested across an estimated 7,261 deals, and

a total of $68.4 billion was invested by early stage VCs in 2022.[7] These investments, and often later round investments (i.e., B and C rounds), are typically used by companies to generate sufficient pre-clinical and Phase I clinical data to attract large scale investment.

Regardless of where they find funding, the focus of an emerging biotech is now on generating a product worthy of investing in a clinical trial while being conscious of both timeline and scalability. At this point, they must consider if they take this all on themselves or enlist the partnership services of a contract development and manufacturing organisation (CDMO). However, they get there, once enough promising and enticing clinical data has been generated to start convincing the market that the technology can deliver on the promises of their drug candidate, the time has arrived to consider and execute an exit strategy.

The emerging biotech may choose to fund later phase clinical trials of a single candidate or fund a therapeutic pipeline while continuing to grow organically. This strategy typically involves making an initial public offering (IPO) to finance the overarching goal of taking drug products to market. Alternatively, and not atypical, the company may choose to exit through a relationship with large pharma. Typical outcomes include partnering, licensing, or full acquisition by a large biopharmaceutical company that will have available resources to enable completion of later phase clinical trials and subsequent commercialisation activities.

Even though this emerging biotech lifecycle has a high rate of attrition, several recent acquisitions, such as the Asklepios Bio acquisition by Bayer, the AveXis acquisition by Novartis, and the Translate Bio acquisition by Sanofi, suggests that this model is successful enough to win continued attention from both VCs and big pharma. A proof-point of the popularity and viability of this approach is the fact that in 2019 the 10 largest biopharma merger and acquisition (M&A) deals were $200 billion in value.[8] In addition, these M&A and partnering activities with small biotech companies have been increasingly used as a growth and sustainment strategy by large pharma. For 2023, this sustainment strategy, combined with a market-induced resetting of biotech valuations, is expected to drive a big year for M&A activities.[8] Further evidence of this strategy by large pharma is the growing number of corporate and academic partnerships leveraged for drug discovery. Here, academic labs are essentially serving the strategic role of a biotech for big pharma. From 2012 to 2016, the number of large pharma academic collaborations has more than doubled to over 25,000.[9]

The Journey of an Innovator

With the goal being IPOs or attracting the attention of a suitor from large pharma, the road to biotech success is riddled with potholes, hurdles, and dead ends. Many biotech companies fail on their journey from conception to partnering with large pharma for multiple reasons and, unfortunately, good science doesn't always translate to the successful management of a program.[10] Clinical failure because of not meeting primary end points in a study or excessive adverse events can mean certain death for an emerging biotech. Chemistry, manufacturing, and controls (CMC) issues that can manifest in drug product heterogeneity or limited drug product availability can also cause companies to fold. In other instances, failure to meet the expectations of the regulators can delay, or all together prevent, clinical studies and push a small company past the reach of its cash runway. Finally, in the case of angel investors or VCs, primary investors may withdraw funding for a variety of reasons, causing cash shortages and failure.

With all the looming obstacles they face, emerging biotechs are motivated to be extremely reactive and agile as speed is the key to success. Time is of the essence since the market and the players know that the attrition rate is high. The C–suite executives of these companies are almost always themselves innovators and early adopters of new technologies, with strong entrepreneurial tendencies and habits. The technical teams they assemble are also highly translational and entrepreneurial. The facilities where these small biotechs operate are usually extremely modest with limited wet lab capabilities. Select companies are fortunate enough to operate out of startup incubators that can offer critical core services including flow cytometry, mass spectrometry, and other analytical methods that typically require dedicated staff and facilities to operate. Others are completely virtual and totally lack wet lab space. All in all, these groups are not stereotypically investing in long-term commercialisation activities, but instead are focused on short-term milestones and goals that will hopefully deliver the next round of funding to lengthen their cash runway and thus ensure survival for a while longer.[6]

CDMOs – an Enabling Resource for Emerging Biotech

Within the described startup lifecycle, these agile emerging biotech companies will at some point need to consider investing in the infrastructure required to scale up, manufacture, and commercialise their innovative drug. Typical facilities and expertise in the areas of process development, manufacturing and quality, and regulatory support will all be required to progress the drug through clinical development. Thus, a critical choice must be made to either build each of these capabilities (staff, equipment, and facilities) inhouse or to buy it through establishing relationships with contract development and manufacturing organisations (CDMOs), such as Aldevron.

Smaller biotech companies, who are already facing a fair amount of risk, are increasingly gravitating toward establishing relationships with CDMOs to improve the probability of success, regardless of intended exit strategy.[11] This trend toward partnering with CDMOs is evidenced in the forecasted growth of CDMO revenues, which are expected to surpass $46 billion by 2025, an increase of more than 40% from 2020.[12] From a risk-mitigation perspective, CDMOs can prevent common issues in both the preclinical and clinical phases of development. In the preclinical phase, processes that are manufacturable and compliant can be efficiently and rapidly scaled up. From a manufacturing perspective, CDMOs offer state of the art facilities and equipment to ensure manufacturing efficiency, consistency, and ultimately successful release of their client's drug product. Operating and maintaining these facilities takes significant resources that an emerging biotech does not have to fully support. As a result, the cash runway can be significantly extended to maximise the chances of survival and eventual success. In addition, small companies may lack adequate experience in all areas of drug product

manufacturing. Thus, leveraging the history of success of a CDMO can facilitate product development through accessing deep expertise and end-to-end capabilities in all facets of drug development. Whether it be through regulatory support during agency engagement, or through accessing advisory support during different phases of product development, CDMOs can offer extensive advice to their clients to avoid potential pitfalls and delays. Finally, establishing a relationship with a CDMO can increase visibility to potential buyers in addition to making the acquisition process smoother overall.

An experienced CDMO partner with varying capabilities can provide tangible value for any company developing a novel nucleic acid-based therapy by sharing valuable lessons learned over the course of hundreds or thousands of clinical trials. Aldevron, for example, has produced more than 165,000 lots of plasmid DNA with nearly 5,000 of them produced at Good Manufacturing Practice (GMP) or GMP-Source® quality over the course of 25 years. Since 2017 Aldevron has also produced more than 70 GMP lots of mRNA drug substance. Altogether, this translates to supporting clients though more than 1,100 clinical trials, forging an understanding of regulatory agencies, fostering the development of new innovations, and incorporating the newest state-of-the-art technologies, which translates to enhanced capabilities for the development of new therapies through the clinical trial path. Where else can an emerging biotech find this level of expertise, experience, and support?

Summary and Conclusions

Novel therapeutic development is moving fast and the biotech industry as a whole is rapidly evolving. Small agile biotech companies are attracting a plethora of new doctorate-level talent and are being sustained through multiple avenues of novel funding mechanisms geared at early phase investment. As a result, emerging biotechs are now the leading innovators of the industry, creating the next generation of life-saving medicines. The life cycle of these companies is equally fast paced with their success dependent on them demonstrating value before their funding is exhausted. Given their focus on demonstrating value quickly to attract additional funding or an exit, these biotech companies are either seeking partnerships with pharma companies in their development, or leveraging the experience, facilities, and expertise of CDMOs to improve their chances of success of drug product commercialisation. Partnering with the right CDMO, such as Aldevron, can provide access to the industry-leading facilities and expertise, which can reduce cost and timelines in multiple facets of product development.

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