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Global Business Reports

U.S. Biopharmaceuticals 2018

PRE-RELEASE EDITION

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U.S. Biopharmaceuticals 2018 Pre-Release

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Dear Readers,

Welcome to the pre-release of the 2018 edition of GBR's U.S. Biopharmaceuticals Report.

The United States is broadly recognized as the global leader in drug discovery and innovation, producing more than half of the world's new molecules in the last decade. Improving patient outcomes through a deeper understanding of disease areas and better-defined addressable patient populations is revolutionizing drug discovery approaches. By not only developing more effective treatments but also matching the right drug to the right patient, companies are driving a new phase of medical progress.

Arguably the most competitive destinations within the United States in terms of attractiveness, our 2018 research has begun with a focus on Massachusetts and California, notably the Boston/Cambridge Area and the San Francisco Bay Area. While the former is lauded for its culture of collaboration, in part attributable to the extreme density of activity, the latter is often cited as the top biotech supercluster due to the sheer volume of activity and high investment figures, both in terms of NIH funding and venture capital.

The following pages present a snapshot of our research thus far in advance of the launch of the final report at the end of April. Until then, our team continues to research top hubs in the United States to provide comprehensive coverage of the U.S. biopharmaceutical industry.

We would like to warmly thank our association partners at MassBio and Biocom for their continued support, as well as to all the executives and researchers who shared their valuable insights.

Catherine Howe
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Innovation Capital

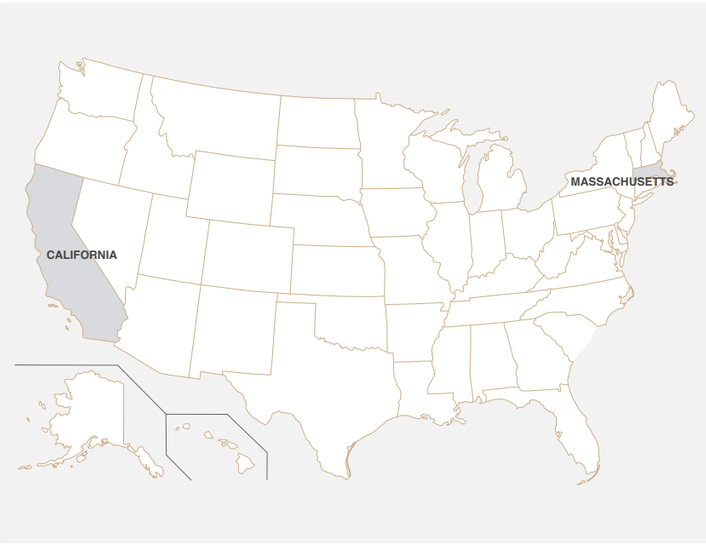
The U.S. biopaharmaceutical industry

Countries around the globe have long placed great emphasis on fostering a competitive life sciences industry. India's focus on generics reflects a need for affordable, accessible medicine, whilst China's growing biotech industry highlights a government focus on driving its technology sectors and meeting the needs of its growing population. The United States, however, has garnered particular attention from overseas as a high value market, and the leader in innovation and drug discovery. Well supported by its favorable IP framework and investment climate, the U.S. pharmaceutical industry accounts for a huge portion of global innovation, producing more than half of the world's new molecules in the last decade.

Within the United States, as innovation has increasingly found its roots in academic institutions and small biotech start-ups, the epicenter of medical progress has shifted away from regions with a historically strong presence of large pharma companies. The tables have in fact turned – it is now the big pharma companies that gravitate towards the fledgling innovative startups and academic institutions with spin-off potential. With the influx of new technology-driven companies into the market, large pharma companies are able to bolster their pipelines through partnership with small biotech companies, whilst themselves bringing additional resources and later-stage development expertise to the table. New Jersey remains notable as the birthplace of several large pharma companies and for the broad range of organizations across biotech, academia, contract services and other supporting industries, but where cutting-edge innovation is concerned, it is California and Massachusetts that today take center stage.

The growth of Massachusetts' life sciences industry has been particularly pronounced in recent years, lessening California's lead as the number one biotech supercluster. The two are now arguably neck-and-neck in terms of attractiveness, with the Boston/Cambridge area often cited as the most conducive to innovation due to its high concentration of companies and culture of collaboration. While different segments of the industry are well represented, the presence of the large research centers of companies such as Sanofi, Pfizer, Biogen and Novartis, alongside a plethora of biotech start-ups, has resulted in a skew towards drug discovery in the Massachusetts area. Shire's current consolidation of its many sites across the state into two main campuses at Cambridge and Lexington will also involve the addition of 100 research jobs as part of the move to root its center of excellence for biopharma research and U.S. business operations in Cambridge.

California still undoubtedly boasts the larger industry by numbers and investment, with employment also more spread out across different disciplines – the California Life Sciences Association's 2018 Report indicates that there are currently 3,249 life sciences companies in the state, with US$6.7 billion in venture capital attracted and US$3.8 billion in NIH grants in 2017. Genentech, part



of the Roche Group, is often ranked first across the fields of biotechnology, oncology and in-vitro diagnostics, and sits in good company with the likes of Amgen and Gilead, which also have their headquarters in the Bay Area.

California is spread expansively over 163,696 square miles and can be subdivided into several clusters, the most prominent being the San Francisco Bay Area, San Diego, Orange County and Los Angeles. “As the birthplace of biotechnology, the Bay Area provides a very strong anchor for the state’s life sciences community,” commented Joe Panetta, president and CEO at Biocom. “The San Diego cluster is as old as the Bay Area’s but has differentiated itself as a leader in cutting-edge technology in therapeutics and research. When the companies grow to a certain size, they increase in attractiveness to larger pharma companies… Because the technology is so attractive, companies tend to be acquired before they have a chance to grow. Every large pharma company has some sort of research outpost in San Diego as a result of acquisitions. San Diego is also the center of the genetic sequencing industry.”

Meanwhile, Orange County has its core strength in medical devices and diagnostics and L.A.’s industry is in its very early stages.

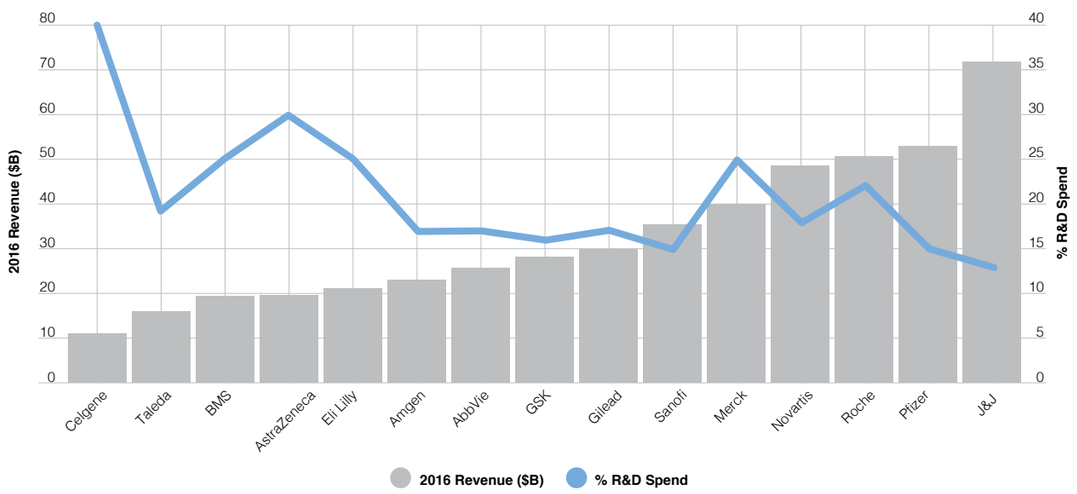
By comparison, Massachusetts received US$2.6 billion in NIH funding and US$2.9 billion in venture investment in 2016 but, in terms of drug discovery, Massachusetts-based companies have demonstrated remarkable efficiency with funds received – whilst California companies currently have 1,274 new therapies in the pipeline, Massachusetts-headquartered companies boasted

"Many of the large pharma companies have felt the need to increase their presence in the Boston/Cambridge area in order to be a part of the innovation activity. Proximity brings a lot of benefits. This industry is highly collaborative with partnership across companies being common and a big driver of success."

-Lain Anderson, Managing Director and Partner, L.E.K. Consulting

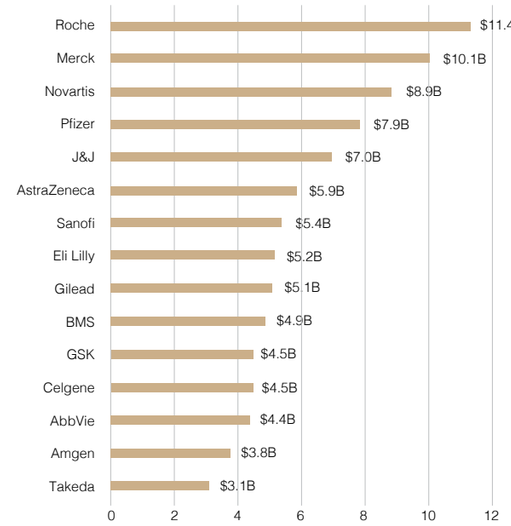
R&D SHARE OF REVENUE 2016

Source: Endpoints News



TOP BIOPHARMA R&D SPENDERS IN 2016

Source: Endpoints News



1,896 drug candidates in 2017, accounting for 19% of the U.S. pipeline and 9% of the global pipeline. Massachusetts’ relatively small geographic area of 10,565 square miles is a key component of its primary advantage, namely the high concentration of companies to be found in the region. The sheer density of activity is greatly conducive to collaboration and, by extension, innovation, whether through knowledge-based partnerships or from a financial perspective. “In the same 10 to 15 square miles, 16 of the top 20 leading biopharma companies, the top 10 leading medical device manufacturers, and the top diagnostics manufacturers can all be found,” commented Travis McCready, president and CEO at the Massachusetts Life Sciences Center. “This is truly quite rare. On top of this we now have all of these companies starting to work with each other which will be very important going forward.”

While geographical distance is by no means prohibitive in an increasingly globalized environment, proximity still holds major advantages. For this reason, although pockets of activity will continue to flourish and germinate across the country, the so-called “biotech superclusters” will continue to garner the most attention both nationally and internationally as destinations for investment and partnership. •

Robert K. Coughlin

President & CEO, Massachusetts Biotechnology Council

MassBio’s mission is to advance Massachusetts' leadership in life sciences to grow the industry, add value to the healthcare system and improve patient lives.

Are there any particular gaps in the market or trends shaping the industry?

There is a significant opportunity around convergence. Today, unlike 10 years ago, the lines between different industry segments such as biotechnology, pharmaceuticals and medical devices are becoming much more blurred. A decade from now, we hope to be the best location in the world for all things life sciences across areas such as drug discovery, cures, combination therapies and companion diagnostics.

We are also seeing huge growth in the diagnostics field. Ultimately, many believe that drugs will not be approved in the future without a companion diagnostic. We want to be able to supply all the components so that precision medicine can become a reality. In addition, we are very excited about digital health. Following on from 2008’s 10-year US$1 billion life sciences initiative, the current state government is rolling out a five-year half-a-billion life sciences initiative with some focus on digital health, contract manufacturing and workforce development.

Which areas of the industry specifically will the new life sciences initiative be targeting?

The initiative will be focused on early stage funding, because company creation is a priority; workforce development, because we need to maintain that world-class pipeline of talent; biomanufacturing, of which we have seen growth but not to the degree of success we believe we can achieve; and there will also be a component to help us capitalize on convergence and advancements in digital health

What are the areas of focus for MassBio going forward?

Drugs and therapies invented in Massachusetts are being used by a patient population of close to two billion worldwide. MassBio’s primary focus is ensuring Massachusetts continues to be the best home for the life sciences industry, and that we have the resources to continue to innovate and serve patients. In Massachusetts, we do not do “me-too” drugs – we pride ourselves on trying to invent what is next.•

"We are not only a biopharma town but we are also a leading cluster in medical device, diagnostics, and digital health sectors. No other region has strength in all these areas. In the same 10 to 15 square miles, 16 of the top 20 leading biopharma companies, the top 10 leading medical device manufacturers, and the top diagnostics manufacturers can all be found. This is truly quite rare."

-Travis McCready,
President & CEO,
Massachusetts Life Sciences Center

MASSACHUSETTS' LIFE SCIENCES SECTOR BY THE NUMBERS

Source: MassBio

500+
Biopharmaceutical businesses

66,414
Life sciences employees

28.2 million
Area of lab space in square feet

5
IPOs from MA-headquartered companies (2017)
-38% of all U.S.- based biotech IPOs

1,896
Drug candidates in development:
19% of US Pipeline,
9% of Global Pipeline

20
Candidates pending FDA approval

$2.572 Billion
NIH Funding in 2016

$2.9 Billion
Venture investment in 2016

Joe Panetta

President & CEO,
Biocom

Representing over 1000 members, Biocom seeks to drive progress in California's life sciences industry.

Could you give a brief introduction to Biocom and its role in California's life sciences industry?

We are in the middle of our five-year strategic plan to position California as the worldwide center for precision medicine. Our focus is to build California's individual life sciences clusters, which primarily include the San Francisco Bay Area, San Diego, Orange County and the greater Los Angeles area, and build bridges between these clusters and others around the world. We have placed a significant emphasis on strategic partnerships in Japan, Australia and France, for example. Every year, we hold a global partnering conference, which involves about 300 life sciences leaders from around the world.

What are the primary contributing factors to the success of these clusters?

The generation of new technology is a big driver in attracting companies to California. We also have a wealth of talent not only on the business side but also the research side – the spectrum encompasses serial entrepreneurs with experience in growing companies and researcher leaders with experience in taking products all the way to commercialization. Companies are attracted by the sheer magnitude of talent, funding, relationships and experience is what brings people here.

What are the main objectives for Biocom in progressing the industry?

Our objective is to continue to raise the visibility for the biotechnology work that is being done here in California and to continue to attract the level of capital required to grow every company. On the policy side, we must continue to ensure a supportive framework in terms of funding and talent to support company growth and progression. Although our clusters are currently strong, there are still areas for improvement. Even with a 40-year history in the Bay Area, our companies still need greater visibility. Biocom's ultimate goal is to accelerate the trajectory of our members largely through building collaborations within the United States and across the globe.•

CALIFORNIA'S LIFE SCIENCES SECTOR BY THE NUMBERS

Source: CLSA

3,249
Life Sciences Companies

919,700
Total Direct, Indirect & Induced Jobs

$113,674
Average Wage

1,274
New Therapies in the Pipeline

440
Medical Devices Approved

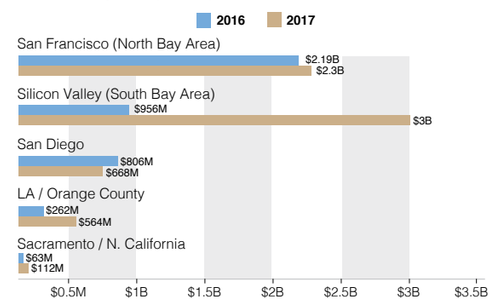
$3.8 Billion
NIH Grants Attracted in 2017, Leading Nation

$6.7 Billion
Venture Capital Attracted in 2017, #1 in the Nation

4,800+
Science and Engineering PhDs Graduated from California Institutions

CALIFORNIA LIFE SCIENCES VC INVESTMENT BY REGION

Source: PwC/CB Insights MoneyTree™ Report



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Finding Funding

The diversification of the biotech financing landscape

As the number of biotech start-ups has rapidly grown and the drug discovery focus has shifted away from the internal pipelines of large pharma companies, the financing landscape has also adapted in line with market needs. While early-stage venture capital funds were once large in number and a primary source of funding for the industry, challenging market conditions have necessitated increasing resourcefulness and a diversification of financing sources. "[F]rom 2000 to 2009, life sciences venture capital was a bad place to be; none of those funds really made much money," commented Peter Parker, managing partner at BioInnovation Capital. "Many changed course and moved towards growth equity, and some carved out their life sciences unit and focused on tech. As a result, there are far fewer early-stage life sciences capital firms, with some being Third Rock Ventures and Flagship Pioneering, which create their own ventures, so follow a different model. This leaves about five in the Boston area and four on the West Coast, and then a large vacuum."

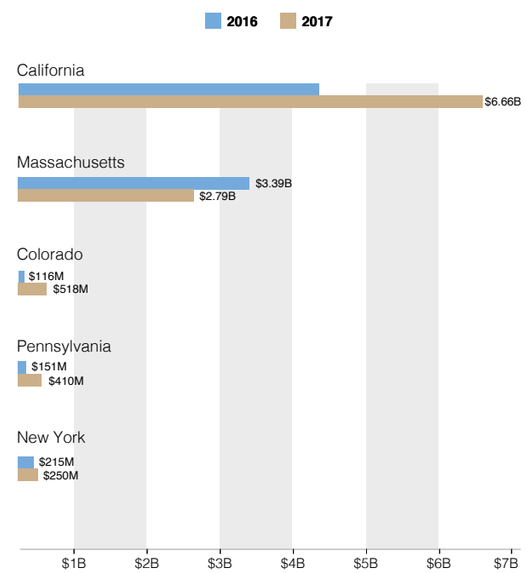
Large pharma companies began to fill this void, establishing their own venture capital funds and fostering relationships with biotechs as an extension of their R&D pipelines. "While these partnerships initially generally favored large pharma, as the biotech industry grew and became more confident, and the value of the research made them more competitive, they were able to demand better terms from the pharma companies, leading to the creation of more balanced partnerships," noted Janice Bourque, managing director at Hercules Capital, a business development company specializing in providing venture debt. "When the stock market fell and the public market with it, many companies were challenged to stay afloat and many venture capital firms fell by the wayside. Since the re-emergence of the public markets, the trajectory has been interesting."

In addition to a range of grants from organizations such as the NIH, there is a large group of angel investors within the Boston and San Francisco communities.

With biotechs seeing increasing support and mutually-beneficial collaboration opportunities from large pharma companies, Massachusetts' companies are particularly well positioned.

TOP 5 STATES FOR LIFE SCIENCES VC INVESTMENTS

Source: CLSA



"Every large pharma company now has a venture capital fund, so some companies get big investments from larger firms. However, many companies do not get that chance. Then, there is a large group of angel investors within the Boston and San Francisco communities. The environment has changed a great deal."

-Peter Parker,
Managing General Partner, BioInnovation Capital and
Co-Founder and Director, LabCentral

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Janice Bourque

Managing Director,
Hercules Capital

Hercules Capital is the largest business development company focused on venture lending.

What makes a company a good investment prospect for Hercules Capital?

Our approach is broad, but we tend to look for companies that have certain characteristics including strong and experienced management teams, a diversified group of institutional investors, an entrepreneurial focus and that are trying to solve big issues in large attractive markets. On the life sciences side, we are generally focused on companies with diversified clinical pipelines and/or companies that have strong platform technologies. Each company is individually reviewed based on growth potential, depending on where it is on its trajectory and what we can do to assist in that growth.

In life sciences, there are so many variables that cannot be measured, so mitigating risk in multiple ways is an absolute necessity. Having a knowledgeable investor is both good for the company and for us as it allows for a partnership approach to anticipating and dealing with risk. Accelerated approval pathways, strategic partnerships, company goals and factors that can reduce cost are good signs. However, we also realize the value in focusing on the management team and how well they execute on a plan and changes to that plan. Understanding the company's exit or growth strategy helps us better understand our role as a partner.

Where would you like to see Hercules Capital positioned in the life sciences industry going forward?

We certainly want to continue to be a world leader in the life sciences space as that evolves. Part of our success is our ability to be flexible and to continue to provide creative product solutions, because as the industry evolves so do its needs. Hercules is the largest venture debt BDC, and we plan to maintain that position. The goal for Hercules is to continue to be a global leader and expand its relationships with other markets and investors.•

Highlighting the importance of the significant presence of 18 of the top 20 pharma companies within the state, Travis McCready, president and CEO at the Massachusetts Life Sciences Center, remarked: "An interesting dynamic is taking place: on a per capita basis we lead the United States in the amount of venture capital being invested into early stage companies… However, unlike in years past, those venture capital dollars are going in larger tranches to a smaller number of companies. The ecosystem has managed to maintain equilibrium because the large pharma and medical device companies have their own investment funds, which amounts to about a billion dollars going into early stage companies. This deployment of investment funds in young companies is not done in any other ecosystem."

Another notable source of financial support are the federal and state governments in the form of incentives and investment into infrastructure. The support of the state government has been a great contributor to the rapid growth of Massachusetts' life sciences sector over the last few years, for example, most clearly reflected in the allocation of a US$1 billion fund, distributed by the Massachusetts Life Sciences Center across three major capital categories as a catalyst for the industry's growth. Half a billion dollars was allocated to capital infrastructure, spanning aspects from research facilities to high-end equipment. Within this category, arguably the most widely acknowledged success has been the LabCentral facility in Cambridge, into which US$10 million was invested. This facility, which provides lab space and resources to its resident companies, contributed to the creation of 402 new jobs and over US$300 million raised in additional financing in 2016 alone, plus the filing of 113 new patents and 27 new licensing agreements.

Of the remaining US$1 billion investment, US$250 million was made available for tax incentives, a huge support in the growth of small and mid-sized companies, and an attractive proposition for companies outside of Massachusetts open to relocating. The final US$250 million was allocated towards an investment fund for pre-seed and seed stage companies, also contributing to internship programs for approximately 500 to 525 high school and college students every year. The Massachusetts Life Sciences Center is now in the process of securing a further half-a-billion dollar investment to be allocated over the next five years.

This strategic allocation of funds, particularly directed towards long-term sustainable growth, puts Massachusetts at a big advantage compared to other life sciences hubs. Other hubs rely more heavily on initiatives and grants directed at particular projects. "One challenge across California is that the industry has had to support its own growth without many incentives provided by the state or federal governments," referenced Joe Panetta, president and CEO at Biocom. "The situation is very different from other hubs such as Massachusetts. State investment in California is generally only through research universities such as UC Berkeley, UC San Francisco, UCLA, UC Irvine, UC Riverside and UC San Diego. 13 years ago, we passed a citizens' initiative, which created our US$3 billion Stem Cell Agency to provide grant funding to academic researchers and small companies within that field."

New Jersey is also particularly committed to creating a favorable framework at a policy level, including a number of financial incentives in support of innovation. For example, the state's recently formed Biotechnology Task Force is charged with the development of recommended action steps that will inform policy making, with the goal of building a first-class innovation economy. By fostering a supportive ecosystem in which start-ups are able to thrive, the potential for bringing novel drugs to market amplifies.

By softening the financial burden, small biotechs are better able to progress focused pipelines, bringing new treatments to market and addressing unmet needs more quickly and efficiently. There is therefore some responsibility at the policy-making level to facilitate innovation where possible, which can also be seen in the formation of biotech incubators. Meanwhile, traditional funding channels continue to drive the industry financially, with venture firms citing cutting-edge innovation as the primary consideration when identifying investment opportunities. •

Defining targets

Maximizing shots on goal

Through a deeper understanding of disease, coupled with novel technologies and approaches, the pharma industry is moving towards more specialized treatments, stepping away from the blockbuster model that has long been the standard, and further towards the discovery of cures. The great overarching theme driving current approaches to drug discovery and development is precision medicine, which incorporates the understanding that every patient is different, both in terms of experiencing a disease, and reacting to a particular course of treatment. According to Clarivate Analytics, the top three areas of therapeutic focus combined represented 56% of investment into the industry in 2017, with cancer accounting for US$80.7 billion, mostly through grants and deals. Neurology/psychiatric treatment was second at US$17.2 billion, followed by immune therapies at US$15 billion. Infection accounted for US$14.3 billion in investment.

Photo courtesy of Northeastern University

A better understanding of disease states and their underlying causes has allowed novel approaches to come to the fore. Biomarkers, for example, have become widely used to monitor and predict the effects of drugs in the human body. As the poster child of precision medicine, mainly due to the large number of intervention points, Oncology research has seen an increasingly narrowed focus in conjunction with the recognition that all cancers are different. "As we develop a greater understanding of the science behind cancer, acceptance increases that not all cancers are the same," stated Richard Peters, president and CEO at Merrimack Pharmaceuticals, a Massachusetts biotechnology company targeting biomarker-defined cancers through 10 wholly-owned programs. "While the primary concern previously centred around the anatomical definition of cancer and this remains important, understanding the molecular signature of the cancer has also increased in importance. The source of the cancer in terms of the organ does not really matter; what really matters is what is making it grow."

Immuno-oncology (I-O) has been a particular area of focus in recent years – an emphasis on getting these new treatments to market has also translated into more favourable pathways. "Because of the much higher efficacy and, in some cases, curative effect of I-O treatments, we have seen development timelines shrink from the typical eight to 10 years to as little as four years or less," highlighted Garo Armen, CEO at Agenus, a clinical-stage biotechnology company focused on progressing its pipeline of checkpoint antibodies, vaccines, and adjuvants, utilizing a number of technology platforms in an integrated approach.

Whilst faster market entry seems very much conducive to medical progress, companies may be challenged to realize ROI targets as efficiently as before due to higher levels of competition within a shorter timeframe. "As development timelines decrease, we will see obsolescence rates go up significantly," continued Armen. "Whereas in the past, companies have had a 10 to 20 year market monopoly, with the potential for many more new market entrants in a shorter time frame, that era has now come to an end… True innovation is rare. We are seeing the same trends in biotechnology that were previously seen in technology. When technology became popular, the market became very crowded because it presented a significant opportunity and therefore attracted a lot of capital. However, only a few companies persisted and prospered long term. The same is starting to happen in biotechnology and particularly in immuno-oncology. Financing is always available. The question is not whether there is enough financing available, but rather is the capital being allocated properly."

Agenus holds an extensive portfolio of checkpoint antibodies, cancer vaccines and cancer microenvironment modifiers. Among the checkpoint antibodies, anti-CTLA-4 and anti-PD-1 antibodies are the key building blocks of the company's combination strategy; it is in multiple clinical trials with combinations. Two additional antibodies – GITR and OX40 – are in clinical trials, in partnership with Incyte.

Despite exciting advances in immuno-oncology, it has become apparent that the treatable patient population size is perhaps smaller than at first projected. "In line with the discovery of the role that the cancer cell plays in protecting itself, the discovery of checkpoint inhibitors is perhaps most significant," emphasized Adelene Perkins, president and CEO at Infinity Pharmaceuticals, an immuno-oncology company developing IPI-549, an oral, once-daily product candidate that selectively inhibits PI3K-gamma. "These inhibitors have shown some stunning results, with almost curative effects. The question then became why we were seeing these profound effects in such a small proportion of patients and why, even in the tumour types in which they work, such as melanoma and head and neck cancer, only between 20% to 40% of patients benefit. Those patients then also often ultimately relapse."

Following research to understand the limitations of checkpoint inhibitors, Infinity discovered the importance of macrophages in supporting the tumour, either playing a pro-tumour or an anti-tumour function. "These macrophages can be specifically reprogrammed, so instead of supporting the tumour they fight it," continued Perkins. "This is mediated by a target. Our team developed a specific inhibitor that can enable the reprogramming of the macrophages from this M-2 function, which is pro-tumour to an anti-tumour M-1 function. Our extensive pre-clinical work showed how reprogramming these macrophages will enable them to fight the tumour and overcome resistance to checkpoint inhibitors. Right now, we are replicating that pre-clinical work in the clinic to show the ability to overcome resistance to checkpoint blockades."

"There are certain advantages to approaching oncology treatment with a smaller molecule. Our goal is to eventually get cancer patients out of the infusion chair. It can be very difficult for patients to make the time to come in every two weeks to receive infusions of the antibody. Our alternative would be to carry a bottle of pills to take throughout the day. That is one of the biggest advantages we see for oral drugs. Another difference is how the two molecules linger in the human body. Antibodies will usually stay in the system for a longer period of time, so side effects that are usually the case with typical infusion must be suffered for several days before the drug leaves the system. Small molecules leave the body in about a day, meaning that unwanted side effects should dissipate much faster than the typical antibody."

-Ali Fattaey, CEO, Curis

Cancer continues to hold the greatest proportion of the life sciences industry's attention. New therapies coming through pipelines place greater emphasis on improving quality of life as a measure of positive outcome as well as ultimate survival.

THE RIGHT DRUG FOR THE RIGHT PATIENT

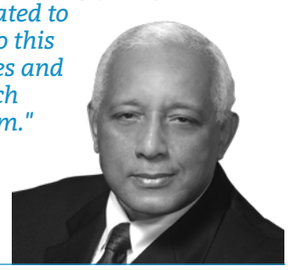
In conjunction with rising drug development costs, regulatory burdens have also increased, resulting in more complex clinical trials. According to PhRMA, after an average development process of 10 to 15 years, only 12% of investigative medicines entering clinical trials are ultimately approved by the FDA. Taking into account that the average cost to develop a new medicine is estimated at US$2.6 billion including the cost of failures, it is clear that the risk is already high.

A better understanding of which patients are most likely to respond to a particular therapy has a huge role to play in aiding the success of trials. "The likelihood of success with a known genetic target, a good molecule and the right patient population is very high," noted Barbara Weber, CEO at Tango Therapeutics, which is focused on identifying novel genetic drug targets for specific cancer subtypes. "I do not know of a situation in which a drug failed with this combination in place. In addition, we can get a good sense of the strength of the clinical signal to expect with pre-clinical models that closely match patient tumours. This approach also makes sense financially because by knowing which patients to address with drugs that have a large therapeutic index, we can expect clinical proof-of-concept in our in Phase 1 studies."

Tango is currently pursuing three areas of drug targets: tumour suppressor gene loss and classic synthetic lethal pairings to drug those tumours; context-dependant oncogenes; identifying drug targets following the development of in vivo systems to define which tumour suppressor genes are mediating immune evasion, leading to the ability to enhance activity of immune checkpoint inhibitors.

"We penetrate the virus with the supercritical fluid and then rapidly expand the system through depressurization... We then thought to reverse engineer the technology to make nanoparticles out of phospholipids, of which cells are made. We now had particles that could encapsulate material to improve their delivery. For example, in cancer, there are many poorly-soluble products which must be nanoencapsulated to improve their bioavailability. We can do this without damaging proteins or molecules and without residual toxins. We have a much safer, sustainable drug delivery platform."

-Trevor P. Castor,
CEO,
Aphios Corporation



The emphasis on targeted treatments and identification of patients with the highest response rates has led to an increasingly prominent role for diagnostic and data analytics companies in drug discovery and development. "With the technology to divide people into those very small and specific groups, we can really start to pinpoint which patients to target for the trial, inform the drug discovery strategy and then gain dedicated patients for life because of this specific selection," commented Loralyn Mears, VP sales and marketing at RowAnalytics, a complex data analytics company specializing in digital health, precision medicine, genomics and semantic search.

According to PhRMA, better use of medicines could eliminate US$213 billion in U.S. health care costs annually, amounting to 8% of the nation's health care costs. In no therapeutic area is this more pertinent than in infectious diseases. As well as unmet needs in the rare infectious disease space, antibiotic resistance is of great cause for concern. "Two factors drive resistance: overutilization and long links of usage for prolonged periods of time," noted Ankit Mahadevia, CEO at Spero Therapeutics, a Cambridge-based biotech focused on treatments for multi-drug resistant (MDR) bacterial infections. "While all drugs will eventually build a resistance, choosing the appropriate populations and using them in the right way helps to delay the onset of resistance."

The importance of developing antibiotics to stay ahead of the bacteria has been manifested through some recent steps to support the progress of research in this area. CARB-X, part of Boston University, was awarded US$250 million in 2016 following a call under the U.S. presidential CARB process for a biopharmaceutical accelerator to support companies in collecting clinical data and attracting outside funding. The organization then recruited the Welcome Trust and NIAID, a NIH division, as part of the process – these each contributed US$155 million and US$50 million respectively. "Groups of academics have been researching antimicrobial resistance for decades, but there have been problems on the business side, including the failure of the normal tools of intellectual property and capital formation to solve the need for new antibiotics," commented Kevin Outterson, CARB-X's executive director. "As soon as an antibiotic leaves the lab, resistance starts to develop. Furthermore, the more we use the antibiotic, whether in livestock or humans, the further the effectiveness degrades. So, it is a maintenance problem. All other drugs may be viewed as an innovation issue, but in the case of antibiotics, a long-term infrastructure and maintenance stance is required."

Backed by CARB-X, Spero is addressing several unmet needs in this space. For example, its SPR994 candidate, the most advanced product in the company's portfolio and currently in Phase 1 trials, is poised to potentially be the first oral carbapenem approved in the United States and European Union. Commenting on resistance to oral Gram-negative antibiotics used to prevent hospitalization and/or help transition the patient home after hospitalization, Mahadevia commented: "Drugs that once filled this void are now seeing resistance at anywhere from 10% to 15% in the community setting and 30% to 35% in the hospital setting. It is a scary proposition to expose these patients to a hospital setting or prolonged hospital visits where even worse bugs exist. This is a multi-billion dollar market and offers a real opportunity to advance in a space that hasn't seen a new oral Gram-negative agent in more than two decades."

Spero's second group of portfolio products, its Potentiator Platform including SPR741 and SPR206, addresses the growing, deadly group of Gram-negative bacteria in the hospital setting needing an IV therapy. Through progressing its pipeline, Spero expects to transition from a Phase 1 company to a Phase 3 company in the next 12 months.

TODAY'S RESEARCH: TOMORROW'S MEDICINE

Research in neurodegenerative disease has also seen an uptick, although recent setbacks may have unsettled current players. In Alzheimer's disease specifically, there have been three significant candidate failures and, in January 2018, Pfizer exited the disease area along with Parkinson's entirely. The market has been dry since Namenda's entry in 2004 and there is still some way to go before candidates currently under development might reach commercialization. MA-based Aphios Corporation is pursuing a differentiated approach to companies such as Eli Lilly and Merck. "There are really three enzymes that effect memory: alpha secretase, beta secretase and gamma secretase," commented Trevor Castor, Aphios' CEO. "These enzymes act on amyloid precursor proteins and form amyloid, which is a neurotoxin that prevents the formation of short-term memories. Inhibiting the beta secretase and gamma secretase enzymes has driven the majority of research thus far. We have gone after alpha secretase, which forms a soluble APP rather than an insoluble amyloid when it acts on amyloid precursor proteins. It works in the opposite mechanism, so our APH compounds up-regulate the alpha secretase to clear out the plaque. We will now have to conduct a Phase 1 and Phase 2 study, which should both be completed in the near future."

Other Alzheimer's drugs in late-stage studies include anti-amyloid antibodies such as Eli Lilly's solanezumab and Biogen/Eisai's aducanumba, and beta secretase inhibitors such as Johnson & Johnson's JNJ-54861911, Novartis/Amgen's AMG-520, Merck's verubecestat and AstraZeneca/Eli Lilly's lanabecestat. Despite challenges and potential loss of attractiveness to drug developers, the Alzheimer's market remains one of the highest unmet need areas in medicine today as the sixth leading cause of death in the United States and nonetheless the only cause in the top 10 without prevention or treatment.

An increasing understanding of disease states has led to a greater emphasis on precision medicine, moving even further into personalized medicine. On par with more effective and even curative treatments, a wider range of options and deeper understanding of the patient are paving the way towards greatly improved outcomes.•

Across the Valley of Death

Bringing academic research into the market

Cited by many as the primary contributing factor in the success of a technology- and research-driven industry, academic institutions cannot be overlooked as a vital driving force of the life sciences industry. The University of California, San Francisco, is California's top recipient of NIH funding, followed by Stanford University, the University of California, San Diego followed by Los Angeles, the University of Southern California and the University of California, Davis, to name a few.

In Massachusetts, universities such as Harvard, MIT, Boston University, Tufts and Northeastern University place a great emphasis on industry collaboration, and have been increasingly recognized by industry as an important and advantageous partner for innovative progress. "Massachusetts did not become the top life sciences hub in the world by chance," stated Robert K. Coughlin, president and CEO at the Massachusetts Biotechnology Council (MassBIO). "There would be no biotechnology or life sciences industry in Massachusetts were it not for the world-class academic institutions and academic medical centers. We have the best and brightest scientists in the world working to develop new, breakthrough cures and treatments. Together with a thriving life sciences industry, there is no unmet medical need known to humankind that somebody in this market is not trying to solve."

The growing number of companies spun out of universities is testament to an increasing emphasis on cutting-edge research as the foundation of medical progress. Universities, too, are better positioned to actualize and commercialize research through collaboration, benefiting from industry support and additional funding opportunities. Equally important are the benefits afforded to students through industry collaborations as an education tool. Northeastern's relationship with industry is particularly proactive, in line with its "Discover, Partner, Innovate" tagline. 97% of its students partake in six-month placements at companies as part of the co-op model.

Identifying a potential gap in the workforce, the university has also begun to push forward its experiential PhD programs, working with companies to jointly develop research programs. "A new area of focus for us is how to educate continual learners," highlighted Ken Henderson, Dean at Northeastern's College of Science. "As technology rapidly evolves, there is a need for the workforce to be retrained and educated in different ways. We are currently looking at how to fill the educational gaps for leading companies and build lasting relationships. We have actually been working with the state legislature to lobby for inclusion of a talent development component within the new life sciences bill. This concerns how to train those people for the highest-level positions and filling in the missing skills gaps."

A recently launched experiential program with GSK exemplifies the enterprise-to-enterprise model. The program is specifically aimed at GSK's current employees that want to get a PhD, and the company considers it as a talent development program. GSK is also seeing it as an opportunity to strengthen ties with a strong research institution. Participants are co-mentored between senior researchers at the company and Northeastern faculty, and may conduct all their research on site at the company. This is an innovative model, which so far is not widely used in the United States.

Academic institutions continue to form the backbone of a great deal of innovation in the life sciences industry. The presence of top universities presents an excellent opportunity for collaboration and, as such, will continue to be a key factor in attracting companies, as well as acting as an ever-growing source of new companies. •

Lean on Me

Contract service segment sees uptick

Outsourcing continues to be an attractive proposition for companies of all sizes for a variety of factors. Partnering with contract service companies to fill gaps in capability or technological expertise is an attractive proposition, often favorable to making acquisitions or building out in-house resources, and in some cases necessary.

Large pharma companies have increasingly looked to outsourcing of core competencies with a view to streamline internal operations and focus on areas of excellence. At the other end of the spectrum, small biotechs often simply lack the in-house capabilities and resources to bring a drug from discovery through to commercialization themselves. "The current worldwide market for outsourcing is about US$5 billion," commented Menzo Havenga, president and CEO at Batavia Biosciences, a company branding itself as a one-stop-shop focused on accelerating the transition of biopharmaceutical product candidates from discovery to the clinic. "Only 12% of the outsourcing market is big pharma, meaning 88% of the market is derived from biotech… The six most important drivers for organizations to consider outsourcing are scale-up, cell line development, medium development, improved yield, new tools testing, and clinical manufacturing. We are active in all these areas and have unique offerings for our client's consideration."

Leveraging its five technology platforms – SCOUT, STEP, SIDUS, SCOPE and SATIRN – Batavia's ambition is to be one of the Top 100 global CDMOs by 2025, reaching US$50 million in revenue by 2025, and doubling its workforce of 120 people. Since offering a full suite of services to clients is highly beneficial, Batavia is likely to pursue an acquisition to expand its clean room facilities and manufacturing capabilities.

"The disadvantage of commercial research, especially in the United States, is the lack of major universities with both clinical capabilities and research capabilities in the same place… Custom procurement and sample processing requires the unique combination of a big clinical center and a research center next to it. Some of our most complex projects are carried out overseas because we need centralized locations to attract patients with rare indications or select patients with difficult criteria – we need a strong patient flow. No single hospital in the San Francisco Bay Area would have sufficient patients for an oncology study. We try to fuse the patient presence with the capability of the center, the presence of the science and the availability of the right scientific talent."

-Olga Potapova, Founder and CEO, Cureline

"We are seeing a lot of investment going into small companies and start-ups, which have their basis in deep research and science. Many of these companies want to be virtual, and therefore do not want to invest in labs or manufacturing or, in general, hardware."

-Manni Kantipudi, CEO, GVK BIO

Alongside favorable trends towards outsourcing is a preference to work with fewer contract service partners, leading to integration of capabilities within the contract service segment. In addition, higher demand means that contract service companies are eagerly positioning themselves to take on a higher number of clients and larger projects. "Because demand is currently exceeding supply, there is a scramble and we see consolidation of organizations and their manufacturing capabilities, especially overseas in developing markets such as China," said Michael Osborne, director of business development at the Boston Institute of Biotechnology, a CRDO specializing in microbial fermentation and mammalian cell culture processes.

Leveraging expertise across both the U.S. and Chinese markets, the Boston Institute of Biotechnology is utilizing accompanying advantages to position itself as a partner of choice to the life sciences industry. "The cost of development and manufacturing is approximately 40% to 50% less than in the United States," continued Osborne. "This alone clearly demonstrates why some U.S. companies might choose to partner with us on some initiatives overseas."

Founded only in 2015, the Institute plans to have manufacturing projects underway in the United States by 2020, and has been manufacturing at its Shanghai facility since December 2017.

Whilst the advantages of different geographies may make some contract service organizations more attractive to their partners, proximity remains important for others and is valued by clients in some cases. In the CRO space, for example, proximity can be hugely important when dealing with biospecimens and patient samples. "In the last 10 years, there has been a greater demand for more information about the patient, and more rapid access to the sample," explained Luke Doiron, CCO at Alabama-based Conversant Bio, which was formed in response to an announcement by the National Cancer Institute that the number-one impediment to the discovery of new drugs was the lack of well-annotated specimens. "Our ability to collect blood samples at a particular point in time, at a particular point in treatment, from a particular patient, is unique. The capability stems from having access to medical records that enable us to find the right patients. Similarly to how CRO's might recruit patients to participate in a drug study, we recruit patients to participate in a blood-collection-only study. As well as being able to carry out overnight delivery in the United States, we also work to ensure that same availability in the other regions that we service."

Conversant Bio plans to expand its cell-based services and conduct biospecimen analysis on behalf of its customers, providing those insights as part of an integrated service.

Contract service companies along the stages of development and manufacturing will continue to consolidate, both in order to take on larger contracts and to provide ever-more integrated service capabilities to their clients.•

Photo courtesy of Batavia Biosciences

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The Winning Formula

Improving patient outcomes

The U.S. innovation landscape is undergoing a fundamental shift in focus away from the blockbuster models that have long been the norm. Improving patient outcomes through a deeper understanding of disease areas and better-defined addressable patient populations is revolutionizing the approach to drug discovery. By not only developing more effective treatments but also matching the right drug to the right patient, companies are reaching for a new phase of medical progress.

Nevertheless, while these new trends feed into a much more favorable environment for the treatment of diseases, the life sciences industry remains a commercial business and reimbursement models are hugely important in maintaining incentives for innovation. Therefore, as the industry moves towards more effective treatments and even cures, it is paramount that the framework evolves in conjunction. Whilst the FDA has in many instances recognized the need for addressing unmet need and accelerating approval timelines, the current U.S. healthcare system's ability to absorb some of these therapies is questionable. "What makes us nervous is the inability of the healthcare system to absorb and measure the costs of curative therapies – both short-term costs and long-term savings," highlighted Bob Coughlin, president and CEO at MassBio. "Currently, we do not have a healthcare system; we have a sick-care system. It is designed to treat chronic sickness with therapies over the life of a patient. If we are going to live in an age of cures, we need a healthcare system and a payer system that can ensure access to these breakthroughs. The way to save money in a healthcare system is by keeping people healthy and out of hospitals and having an accounting system that tracks costs avoided when new drugs come to market. The clock is ticking, and we need to continue to work together as an industry to come up with a new system, or the government will do it for us and get it wrong. We need the payer system to innovate at the same rate at which we innovate on the discovery and manufacturing side."

In response to this flaw in the system, MassBio has initiated a working group with payers and market access representatives from its member companies to continue to build value-based partnerships and other innovative methods of paying for new therapies. Coughlin added: "We are taking the argument of drugs being too expensive off the table; drugs save money by keeping people out of the hospital and actually only account for 12% of the total cost of healthcare. Restricting access to patients is not an option, so the only solution is to find new ways to cover the costs of these drugs."

In an industry that holds the improvement of patient health and quality of life at its core, working together towards a common goal is a logical step in advancing treatment options and discovering cures. This includes dialogue across all aspects of the industry, from the commercial players to the associations, in many instances acting as policy advocates and the policy makers themselves.

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