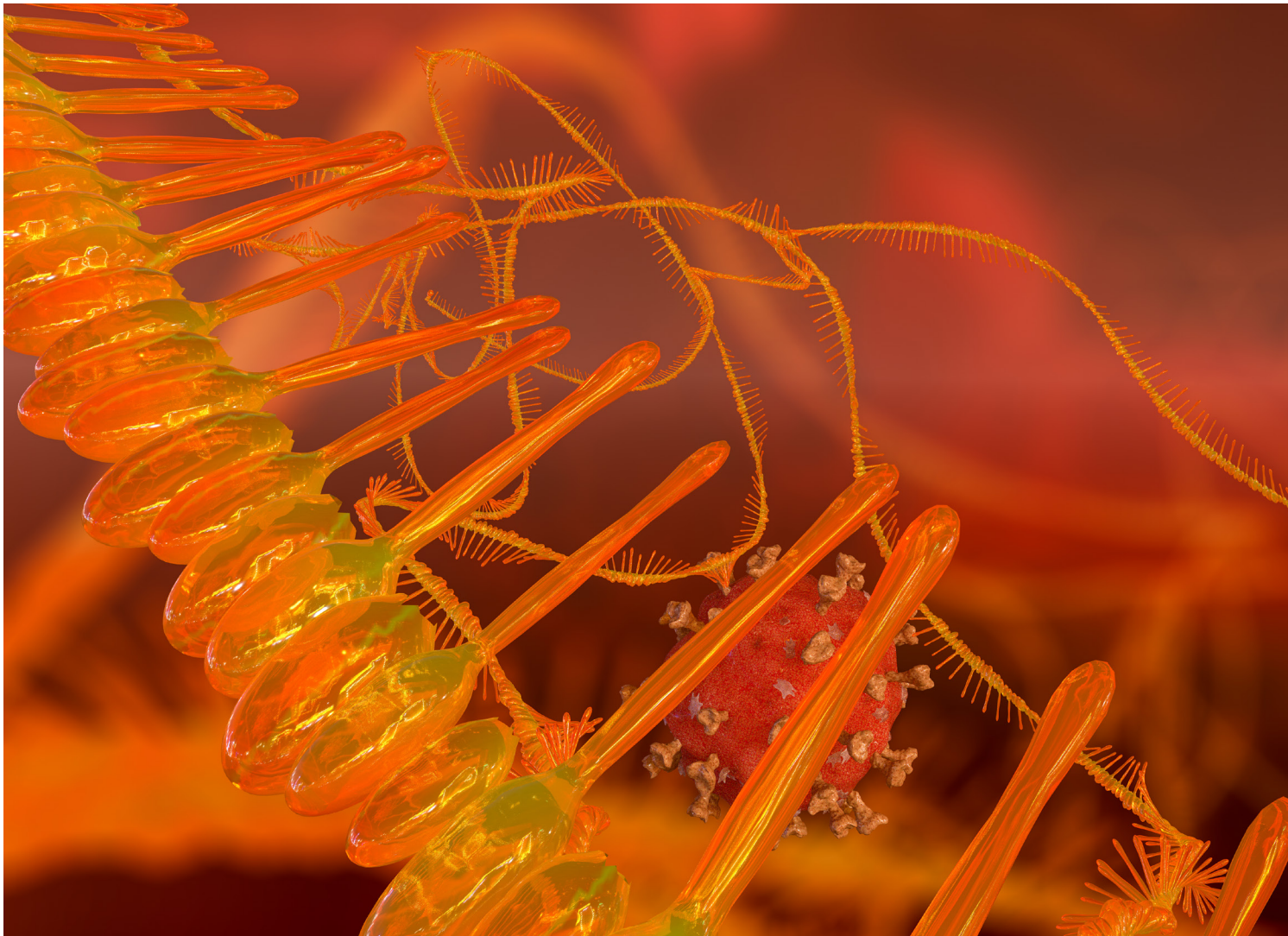
GENEDGE

A-LIST COMPILATION

2021

Six of the Best Reports from the Front Line of Biotechnology



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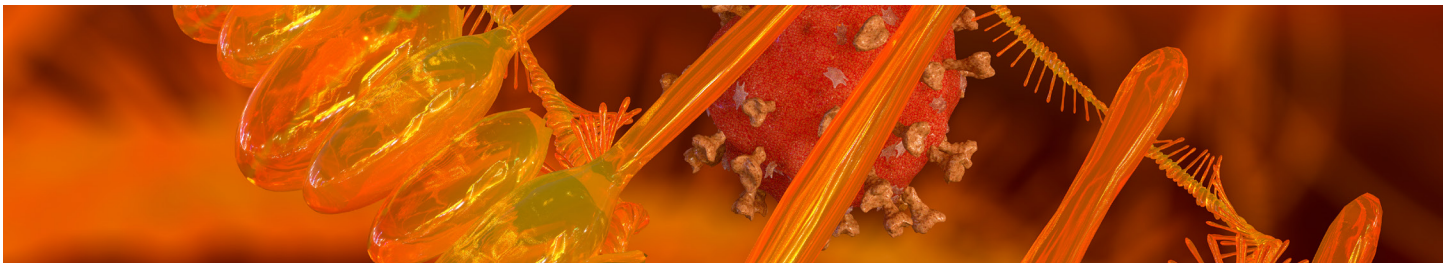


2021

Six of the Best Reports from the Front Line of Biotechnology

To mark the end of 2021 — the first full year in which we have been publishing exclusive news and commentary in *GEN* Edge — we are publishing a special report that gathers six of the most important and memorable A-Lists posted this year.

At the start of the year, *GEN* reported on "hope for an eventual end to the COVID-19 pandemic" based on the rollout of the first vaccines and drugs against the virus, one of "Seven Biopharma Trends to Watch in 2021." But a series of variants, especially Delta, and resistance to vaccination and other public health measures based on religious and other reasons kept COVID-19 hanging around in 2021, and most probably into 2022 and beyond.

That did not stop biopharmas from generating millions of dollars, sometimes billions, from their COVID-19 vaccine and drugs, according to three A-Lists compiled by *GEN* during 2021. The most recent list, which recorded the Top 11 Best Selling COVID-19 Vaccines and Drugs of H1 2021, is among six A-Lists from 2021 republished here for GEN Edge subscribers as a snapshot of biopharma business activity.

Among those six is an additional A-List focused on COVID-19. The spread of the virus touched off a scramble to develop vaccines, with a half-dozen of them showing enough promise by the fall to warrant inclusion among Six Up-and-Coming COVID-19 Vaccines.

During 2021, *GEN* also updated its A-List of Top 10 U.S. Biopharma Clusters, a nationally-quoted ranking of the nation's top life sciences hotspots that was cited this year by news outlets such as the *Boston Globe* and think tanks that included the Milken Institute.

The cluster list draws upon criteria that include the number of jobs. This year, *GEN* also updated its list of Top 10 Life Sciences Jobs Most in Demand over the Next Decade, namely research and clinical biotech occupations projected to add jobs through 2029, according to the U.S. Bureau of Labor Statistics' Occupational Outlook Handbook.

Also republished here are A-Lists highlighting two fast-growing sectors of biopharma. One is *GEN's* Top 10 RNA-Based Biopharmas, which updates a ranking first compiled in 2018, before billions of doses of mRNA-based vaccines were administered to prevent COVID-19.

James Lambeau

Alex Philippidis

The other list, "Top 10 Synthetic Biology Companies," for example, would have been compiled differently if published today. That list, first published in July, included eight "Up and Comer" companies. One of them was Zymergen, based on an initial public offering (IPO) in April that generated $529.6 million in net proceeds—at the time, the largest-ever IPO for a synthetic biology company.

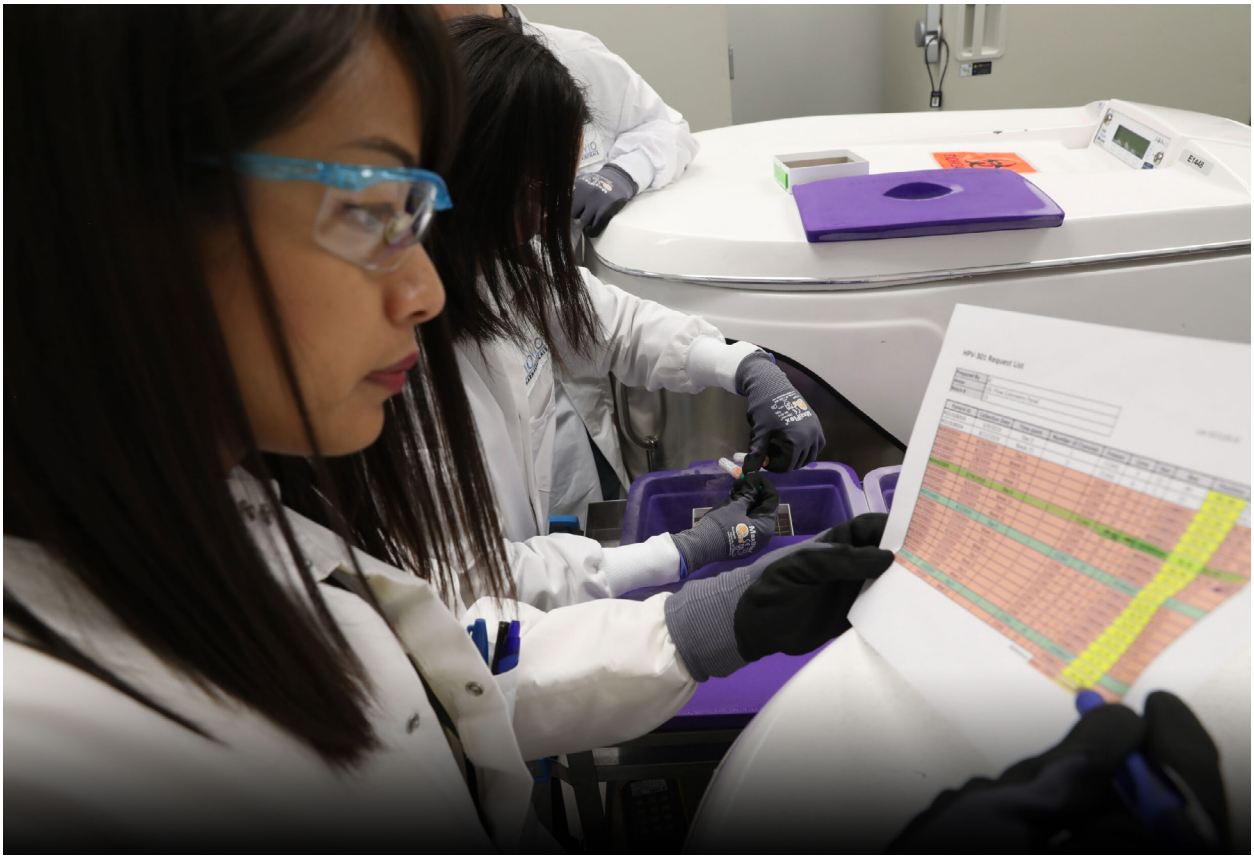
Just four months later, Zymergen shares plunged 68% and the CEO resigned. Six weeks later, Zymergen was bested on Wall Street by an even bigger synthetic biology IPO—that of Ginkgo Bioworks, which went public on September 17 through a merger with a special purpose acquisition company (SPAC) that valued the company at $15 billion. The combination provided Ginkgo total proceeds of more than $1.6 billion.

On behalf of the entire GEN Edge team, thank you for subscribing to GEN Edge -- GEN's premium content tier offering in-depth coverage of biopharma business and key opinion leaders across the industry. We hope you enjoy a happy and prosperous 2022, a year where we finally fulfill the "hope for an eventual end to the COVID-19 pandemic."

Alex Philippidis
Senior Business Editor

Six Up-and-Coming COVID-19 Vaccines

Besides Pfizer/BioNTech, Moderna, and J&J, many other biopharmas have jabs in the clinic that have shown significant protection against SARS-CoV-2



Inovio Pharmaceuticals is preparing to launch the global Phase III segment of its Phase II/III INNOVATE trial (NCT04642638) evaluating INO-4800, a DNA vaccine targeting the major surface antigen spike protein of SARS-CoV-2. Interim efficacy results are expected in 2022.

Since the start of the COVID-19 pandemic, the response from public health agencies, regulators, researchers, and industry has been dominated by the development of vaccines. As of October 14, McGill University's McGill COVID19 Vaccine Tracker listed 153 vaccines in clinical development, of which 23 had been approved or authorized for emergency use in at least one country.

In the United States, the FDA has approved one COVID-19 vaccine (Pfizer/BioNTech's Comirnaty) and authorized for emergency use two others (Moderna's Moderna COVID-19 Vaccine and Johnson & Johnson's Janssen COVID-19 Vaccine). Beyond the United States, most approvals and authorizations have been granted to those vaccines and others developed by AstraZeneca/University

of Oxford (122 countries), Sinopharm (65), Sinovac Biotech (40), Russia's Gamaleya Research Institute (16), and CanSino Biologics (9).

Six COVID-19 vaccines that have shown positive data and/or regulatory progress in recent months are highlighted in this article.

Covaxin

Ocugen (Malvern, PA) is participating in regulatory reviews with the FDA and Health Canada for Covaxin, the vaccine the company is co-developing in both countries with Bharat Biotech (Hyderabad, India). In a preprint posted in July, researchers from Bharat and partners showed Covaxin to have 77.8% efficacy in mild, moderate, and severe COVID-19 disease; 93.4% against severe COVID-19 disease alone; and 65.2% against the Delta variant, in a trial that enrolled 25,798 participants aged 18–98 in India.

"Covaxin is the only product with controlled clinical trial efficacy data on the Delta variant," Shankar Musunuri, PhD, MBA, Ocugen chairman, CEO, and co-founder, told *GEN*. The point here is that the data for Covaxin is not limited to neutralization data extrapolated from laboratory studies. (Pfizer/BioNTech, Moderna, and other developers have launched trials of reformulated vaccine candidates designed to generate clinical efficacy data vs. Delta.)

Covaxin is a whole-virion, inactivated COVID-19 vaccine formulated with a toll-like receptor 7/8 agonist molecule (IMDG) and Alhydroxiquim-II, an NIH-funded adjuvant discovered by ViroVax. Covaxin has received emergency authorization in 16 countries including India, with emergency applications pending in more than 60 additional countries.

Ocugen is seeking FDA guidance on pursuing a biologics license application. "As soon as we reach an agreement on how to bridge some additional trials, we'll do that and work closely with the FDA," Musunuri said.

Bharat Biotech developed Covaxin with the Indian Council of Medical Research, National Institute of Virology.

GBP510

SK Bioscience (Seongnam-si, South Korea) and GlaxoSmithKline (GSK; Brentford, United Kingdom) launched a Phase III trial of GBP510 in August. For this trial, the plan is to administer GBP510 with GSK's pandemic adjuvant to more than 4,000 participants.

"Recruitment is progressing well," a GSK spokesperson told *GEN*. "Results are expected in the first half of 2022, after which, subject to regulatory approval, we hope to supply the vaccine at scale worldwide through the COVID-19 Vaccines Global Access (COVAX) Facility."

Earlier this year, SK and GSK reported positive interim Phase I/II results showing a 100% seroconversion rate, with all participants who received the adjuvanted vaccine candidate developing strong neutralizing antibody responses. Neutralizing antibody titers were between five and eight times higher than sera from people who had recovered from COVID-19.

GBP510 combined with GSK's adjuvant is a self-assembled nanoparticle vaccine candidate targeting the receptor binding domain of the SARS-CoV-2 spike protein. SK is developing the antigen with the Institute for Protein Design at the University of Washington with support from the Bill and Melinda Gates Foundation and the Coalition for Epidemic Preparedness Initiative (CEPI) as part of the Wave 2 vaccine investment project to develop more accessible and affordable COVID-19 vaccines.

INO-4800

Inovio Pharmaceuticals is preparing to launch the global Phase III segment of its Phase II/III INNOVATE trial (NCT04642638) evaluating INO-4800, a DNA vaccine targeting the major surface antigen spike protein of SARS-CoV-2. Interim efficacy results are expected in 2022.

Inovio has reported complete maintenance of both CD4+ and CD8+ T-cell responses against all variants of concern tested, including Delta. "The broad T-cell responses that we are generating with 4800 give us confidence that we can protect against the known variants—Alpha, Beta, Gamma, and Delta—but also potentially the as-yet-unknown future variants," Kate E. Broderick, PhD, senior vice president, R&D, Inovio, told *GEN*.

INNOVATE will be conducted with Advaccine Biopharmaceuticals Suzhou, which holds exclusive rights to develop, manufacture, and commercialize INO-4800 within Greater China. INNOVATE is set to recruit participants across Latin America, Asia, and Africa (numbers will vary depending on regional infection rate)—though not the United States, where the trial remains on partial clinical hold because the FDA has raised questions about the Cellectra 2000 device used for delivering INO-4800.

"We will be gathering data and look forward to working with the FDA to get off the hold," Broderick added. Afterward, Inovio plans to file a biologics license application using efficacy from the INNOVATE trial.

NVX-CoV2373

Novavax (Gathersburg, MD) told *GEN* it expected to seek an emergency use authorization from the FDA for NVX-CoV2373 during the fourth quarter. Outside the United States, Novavax and partner Serum Institute of India have submitted their first emergency use filings in India, Indonesia, and the Philippines, as well as an application for emergency use listing with the World Health Organization. Novavax added that it was working to complete ongoing rolling submissions to the World Health Organization and regulators in Europe, the United Kingdom, Canada, Australia, and New Zealand.

"Our first doses are committed to the developing world, and our largest customer is the COVAX Facility, with a cumulative 1.1 billion doses committed in partnership with the Serum Institute of India," a Novavax spokesperson said.

Novavax in June reported robust data from its pivotal Phase III PREVENT-19 trial (NCT04611802), which showed 90.4% efficacy against mild, moderate, and severe disease; 100% protection against moderate and severe disease; 91% efficacy among high-risk populations; 92.6% efficacy against variants of concern/interest; and 100% efficacy against variants not classified.

More recently, Novavax launched a clinical study assessing a combination vaccine (NVX-CoV2373 and NanoFlu) against COVID-19 and influenza. "The combination vaccine positions Novavax to address a future need to annually immunize against both SARS-CoV-2 and influenza virus, potentially in advance of the winter transmission season," Novavax noted. "It will not impact the ongoing and future standalone studies of our COVID-19 and NanoFlu vaccines."

SCB-2019 (CpG 1018/Alum)

Clover Biopharmaceuticals (Chengdu, China) and Dynavax Technologies (Emeryville, CA) reported in September that their protein-based COVID-19 vaccine candidate SCB-2019 (CpG 1018/Alum), in combination with Dynavax's CpG 1018 adjuvant, met the primary and secondary efficacy endpoints in the global Phase II/III SPECTRA trial (NCT04672395), a trial that enrolled more than 30,000 participants in the Philippines, Brazil, Colombia, South Africa, and Belgium.

SCB-2019 (CpG 1018/Alum) showed 100% efficacy against severe COVID-19 and hospitalizations, and 84% efficacy against moderate-to-severe COVID-19 caused by any strain of SARS-CoV-2; all strains in the study were of variants. Clover also reported 79% overall efficacy against COVID-19 of any severity caused by Delta, 92% against Gamma, and 59% against Mu.

"Based on our pioneering data, we believe that SCB-2019 (CpG 1018/Alum) could be utilized as an important tool to combat this pandemic," stated Joshua Liang, CEO, Clover. "We remain dedicated to expediting the availability and equitable access of our COVID-19 vaccine candidate for global distribution."

The vaccine combines SCB-2019 antigen, a stabilized trimeric form of the S-protein (S-Trimer) based on the original strain of the SARS-CoV-2 virus, with CpG 1018 and alum.

VBI-2902

VBI Vaccines (Cambridge, MA) said in June that its enveloped virus-like particle vaccine VBI-2902 showed proof of concept by generating initial positive data in the Phase Ia portion of a Phase I/II trial (NCT04773665). Data showed that a 5 µg dose expressing an optimized form of the SARS-CoV-2 spike antigen and adjuvanted with aluminum phosphate induced neutralization titers in 100% of participants, with 4.3 times the geometric mean titer (GMT) compared to convalescent sera.

After two doses, VBI-2902 induced antibody binding titers in 100% of participants, with a geometric mean titer of 4,047 units/mL, 5.0 times the geometric mean titer of the convalescent serum panel.

"We achieved a human proof of concept at a very low dose using simply alum, which has been in tens if not hundreds of millions of people," Jeff Baxter, VBI's president and CEO, told *GEN*.

"A two-dose regimen makes sense," added David E. Anderson, PhD, VBI's co-founder and chief scientific officer. "In terms of the 5 µg dose, we were very pleased with the kind of potency we saw. We are encouraged by the validating data seen to date from VBI-2902."

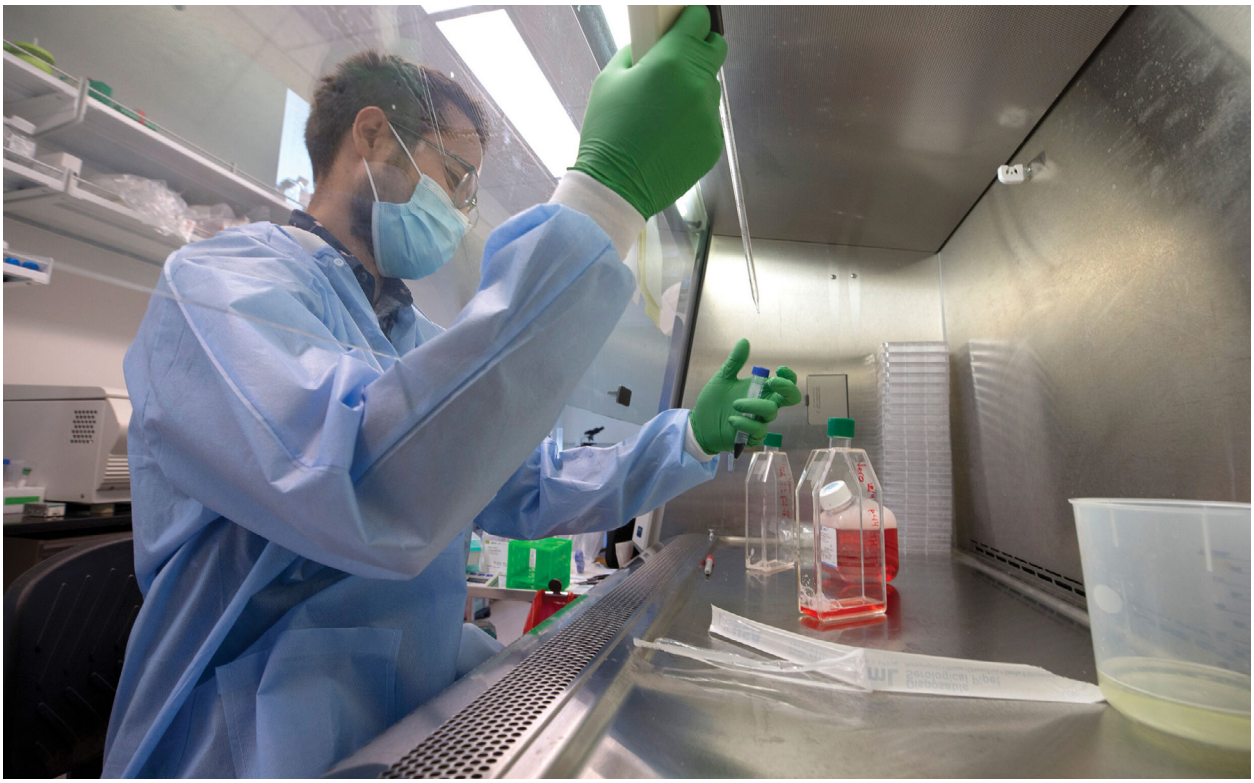
VBI-2902 is one of three enveloped virus-like particle vaccine candidates that VBI Vaccines is developing. In September, the company began a clinical study of VBI-2905 as a two-dose course and as a single booster dose against variants of concern including Beta and Delta. "Our biggest concern is understanding the extent to which the VBI-2905 booster can really give us protective immunity across the landscape of variants that are currently circulating," Anderson noted.

During the first half of 2022, VBI Vaccines expects to launch its first clinical study of its trivalent pancoronavirus vaccine candidate VBI-2901, expressing the SARS-CoV-2, SARS-CoV, and MERS-CoV spike proteins.

Top 11 Best Selling COVID-19 Vaccines and Drugs of H1 2021

Total sales for top sellers rocket to $36.9B in January–June, more than triple Q1 and nearly 9x 2020 totals

Source: Karen Ducey/Getty Images



The debate over whether and how broadly to approve additional "booster" doses of COVID-19 vaccines is expected to play out this month. This much is certain: The FDA's Vaccines and Related Biological Products Advisory Committee will discuss whether to recommend booster doses for the Pfizer/BioNTech COVID-19 vaccine (COMIRNATY®, BNT162b2) meets on September 17.

After that, it's anyone's guess what will happen. The FDA typically follows the recommendations of its advisory panels—as it did last December when it granted an emergency use authorization (EUA) for Pfizer and BioNTech, followed a week later by an EUA for Moderna (mRNA-1273, marketed in Europe as Spikevax®), and in February by an EUA for Johnson & Johnson (Janssen Pharmaceutical Cos)'s single-shot COVID-19 vaccine.

However, the FDA's acting commissioner Janet Woodcock, MD, has joined Rochelle P. Walensky, MD, MPH, direc-

tor of the Centers for Disease Control and Prevention, in urging President Joe Biden's administration to postpone a plan they helped draft, and which he announced August 18—to begin distributing booster doses of COVID-19 vaccines starting the week of September 20.

According to *The New York Times*, which cited unnamed sources, Woodcock has since maintained privately that setting a firm date to start the booster shots was risky until regulators have thoroughly reviewed data in support of that decision.

The booster doses would add to the billions Pfizer, BioNTech, and Moderna have reaped from their COVID-19 vaccines this year, and should reap again next year: "We expect Pfizer/BioNTech and Moderna could each see annual sales of roughly $2 billion," Morningstar analyst Damien Conover wrote August 18. Morningstar has projected strong vaccine sales for Pfizer/BioNTech ($35 billion in 2021 and $39 billion in 2022) and Moderna ($21 billion in 2021 and $22 billion in 2022), with growth expected to come from sales in developing markets and third-dose booster sales in the U.S. and other developed markets.

The Pfizer/BioNTech and Moderna vaccines accounted for 70% of the total combined $36.907 billion in sales generated during January-June 2021 by the top-selling 11 COVID-19 vaccines and drugs for which sales figures have been disclosed (or in the case of one company, suggested in an investor presentation)—and compiled by *GEN* in this A-List.

Each drug or vaccine is listed by its name(s), sponsor(s), first half 2021 sales as disclosed by sponsor(s), U.S. sales, second-quarter 2021 sales, and the sponsors' 2021 sales guidance to investors, with a comparison to forecasts as of the first quarter where available.

Total COVID-19 vaccine and drug sales of the best sellers have rocketed from the $10.91 billion in sales tallied in *GEN's* A-List of Q1 2021 best sellers, and especially from the $4.23 billion in *GEN's* 2020 best sellers A-List.

Unlike those previous lists, this latest list of COVID-19 best-sellers could not include CoronaVac, the vaccine developed by Sinovac, since at deadline the company had not released results for either the first or second quarters of 2021. However, an investor with a 15% stake in Sinovac, Sino Biopharmaceutical, reported a six-fold year-to-year jump in net income, to RMB 8.48 billion ($1.3 billion), with Sinovac and other associated companies and joint ventures contributing RMB 6.91 billion (about $1.1 billion) of that total: "A glimpse into the windfall made during the coronavirus pandemic by the Chinese vaccine developer," Bloomberg News reported.

Some companies with vaccines and drugs in development are already recording sizable revenue from them. Novavax, for example, said it has generated $745.246 million in the first six months of 2021 ($298.017 million during Q2), which the company said reflected development activities relating to its vaccine NVX-CoV2373 for services performed under the U.S. government and Coalition for Epidemic Preparedness Innovations agreements.

This list does not include numerous additional COVID-19 vaccines and drugs that are well into clinical development but have yet to win any approvals or emergency authorizations from regulators. More than 300 vaccines and drugs are in development for COVID-19, according to *GEN's* COVID-19 DRUG & VACCINE CANDIDATE TRACKER.

Top Public Companies

11. Sotrovimab (formerly VIR-7831, also called GSK4182136)

Sponsors: GlaxoSmithKline (GSK) and Vir Biotechnology
H1 2021 Sales (Worldwide): £16 million ($22 million) [1]
U.S. Sales: $0 (0%)
Q2 2021 Sales: £16 million ($22 million) [1]
Guidance (Change from Q1 2021): N/A

10. Regkirona® (regdanvimab; CT-P59)

Sponsor: Celltrion Healthcare
H1 2021 Sales (Worldwide): KRW 43.7 billion ($37.6 million) [2]
U.S. Sales: $0 (0%)
Q2 2021 Sales: KRW 34.5 billion ($29.7 million) [2]
Guidance (Change from Q1 2021): N/A

9. Single-Shot COVID-19 Vaccine (formerly JNJ-78436735, Ad26.COV2.S)
Sponsor: Johnson & Johnson (Janssen)
H1 2021 Sales (Worldwide): $264 million
U.S. Sales: $151 million (57%)
Q2 2021 Sales: $164 million
Guidance (Change from Q1 2021): N/A

8. Olumiant (baricitinib) [3]
Sponsor: Eli Lilly
H1 2021 Sales (Worldwide): $402.2 million [3]
U.S. Sales: $42.5 million (about 11%)
Q2 2021 Sales: $284.7 million
Guidance (Change from Q1 2021): N/A

7. Bamlanivimab and **etesevimab** [4]
Sponsor: Eli Lilly
H1 2021 Sales (Worldwide): $959.1 million
U.S. Sales: $734 million (76.5%)
Q2 2021 Sales: $148.9 million
Guidance (Change from Q1 2021): $1 billion to $1.1 billion, down from $1 billion to $1.5 billion [5]

6. Pandemic COVID-19 Vaccine (marketed in some countries as Vaxzevria or Covishield; formerly AZD1222)
Sponsors: AstraZeneca and Serum Institute of India
H1 2021 Sales (Worldwide): $1.135 billion [6]
U.S. Sales: $0 (0%)
Q2 2021 Sales: $862 million [6]
Guidance (Change from Q1 2021): N/A [7]

5. Actemra® / RoActemra® (toclizumab)
Sponsors: Roche and Genentech, a Member of the Roche Group
H1 2021 Sales (Worldwide): CHF 1.642 billion ($1.789 billion) [8]
U.S. Sales: CHF 689 million ($751 million)
Q2 2021 Sales: CHF 863 million ($940 million)
Guidance (Change from Q1 2021): N/A

4. Veklury® (remdesivir)
Sponsor: Gilead Sciences
H1 2021 Sales (Worldwide): $2.285 billion
U.S. Sales: $1.236 billion (54%)
Q2 2021 Sales: $829 million
Guidance (Change from Q1 2021): Between $2.7 billion and $3.1 billion, up from between $2 billion and $3 billion

3. REGEN-COV™ / Ronapreve™ (casirivimab/imdevimab)
Sponsors: Regeneron Pharmaceuticals (REGEN-COV) and Roche (Ronapreve)
H1 2021 Sales (Worldwide): $4.156 billion [9]
U.S. Sales: $2.853 billion (69%) [10]
Q2 2021 Sales: $3.528 billion [11]
Guidance (Change from Q1 2021): After forecasting approximately $2.9 billion earlier this year, based on a U.S. government contract 10, Regeneron said it expects only $34 million in U.S. net product sales during Q3 relative to the agreement. "U.S. net product sales of REGEN-COV in the fourth quarter of 2021 will be dependent upon acceleration of COVID-19 cases and related drug utilization," Regeneron said August 5 in announcing its Q2 results.

2. Moderna COVID-19 Vaccine (mRNA-1273; Spikevax™ in Europe)
Sponsor: Moderna
H1 2021 Sales (Worldwide): $5.93 billion [12]
U.S. Sales: $3.451 billion (58%)
Q2 2021 Sales (Worldwide): $4.197 billion [13]
Guidance (Change from Q1): ~$20 billion, up from $19.2 billion

1. COMIRNATY® (BNT162b2)
Sponsors: Pfizer and BioNTech
H1 2021 Sales (Worldwide): $19.927 billion [14]
U.S. Sales: $4.072 billion (20.5%) [14]
Q2 2021 Sales (Worldwide): $14.077 billion [15]
Guidance (Change from Q1): $52.3 billion consisting of $33.5 billion projected by Pfizer and €15.9 billion ($18.8 billion) projected by BioNTech—up from approximately $41 billion consisting of $26 billion (Pfizer) and ~€12.4 billion ($14.7 billion; BioNTech) [16]

References

1. Vir Biotechnology also reported $5.333 million in collaboration revenue from its profit-sharing arrangement with GlaxoSmithKline (GSK) for the sale of sotrovimab under Vir's 2020 agreement with GSK. Vir's contractual share of 72.5% from the sales of sotrovimab is based on revenue reported to Vir by GSK, net of cost of sales and allowable expenses (including distribution, selling and marketing expenses) in the period. GSK receives the remaining 27.5% for sotrovimab. VIR oversees development of the antibodies while GSK is responsible for commercialization and books all sales. Vir also recognized $0.9 million of royalties due to Xencor from the sale of sotrovimab.

2. Celltrion Healthcare furnished sales results for Regkirona by disclosing the monoclonal antibody's percentage of the company's total sales for the first and second quarters of 2021. In its presentation to analysts of second quarter 2021 results, Celltrion disclosed that Regkirona accounted for 8% of the company's sales of KRW 431.8 billion ($372.9 million), which would be approximately KRW 34.5 billion ($29.8 million); and 2% of Celltrion's Q1 sales of KRW 457 billion ($394.6 million) in Q1 sales, which would come to about KRW 9.14 billion (about $7.9 million).

3. The FDA on November 19, 2020, issued an Emergency Use Authorization (EUA) for the distribution and emergency use of Olumiant® (baricitinib) in combination with Gilead Sciences' Veklury® (remdesivir) in hospitalized adult and pediatric patients two years of age or older with suspected or laboratory confirmed COVID-19 who require supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). On July 28, the FDA expanded its EUA for Olumiant as a COVID-19 treatment by allowing the drug's use with or without Veklury.

4. Effective Q1, Lilly began reporting sales of its COVID-19 antibodies as a single entity, "COVID-19 Antibodies," consisting of both sales for bamlanivimab administered alone (which were furnished during the fourth quarter of 2020) as well as sales for bamlanivimab and etesevimab administered together, pursuant to FDA Emergency Use Authorizations.

5. Lilly said its reduced guidance reflected excess inventory charges "primarily due to the combination of changes to current and forecasted demand from U.S. and international governments and near-term expiry dates of COVID-19 antibodies."

6. Sales figures for the first half of 2021 and second quarter of 2021 do not include $33 million of collaboration revenue also reported by AstraZeneca from its licensing partner for manufacturing the vaccine and supplying 1 billion doses for low- and middle-income countries, the Serum Institute of India, which markets the vaccine under the name COVISHIELD™.

7. AstraZeneca did not furnish revenue or profit guidance for its COVID-19 vaccine in its second-quarter results, as it was expected to do earlier this year: "In general, AstraZeneca continues to recognise the heightened risks and uncertainties from the effects of COVID-19, including the impact from potential new medicines for COVID-19 in clinical development," the company said July 29 in announcing Q2 results.

8. In reporting a 16% year-over-year sales increase for Actemra® and RoActemra® (tocilizumab) during the first half of 2021, Roche stated: "Growth was driven by the fact that a number of countries included this medicine in their treatment guidelines for severe COVID-19-associated pneumonia." One of those countries was the U.S.: The FDA on June 24 granted emergency use authorization (EUA) to Genentech for intravenous Actemra for the treatment of COVID-19 in hospitalized adults and pediatric patients (2 years of age and older) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

9. Total sales for the first half of 2021 consisted of $3.508 billion for REGEN-COV and CHF 595 million ($648 million) for Ronapreve.

10. Total U.S. sales for the first half of 2021 consisted entirely of sales of REGEN-COV, and included $2.6 billion in Q2 U.S. sales from the manufacture and delivery of 1.25 million doses to the U.S. government, fulfilling the company's entire supply contract with the Biomedical Advanced Research and Development Authority (BARDA).

11. Total sales for the second quarter of 2021 consisted of $3.061 billion for REGEN-COV and CHF 429 million ($467 million) for Ronapreve.

12. Total sales for the first half of 2021 based on the sale of 302 million doses.

13. Total sales for the second quarter of 2021 based on the sale of 199 million doses.

14. Total sales for the first half of 2021 consist of $11.3 billion from Pfizer and €7.282 billion ($8.627 billion) from BioNTech. U.S. sales during H1 2021 were reported by Pfizer from "BNT162b2 alliance revenues and direct sales."

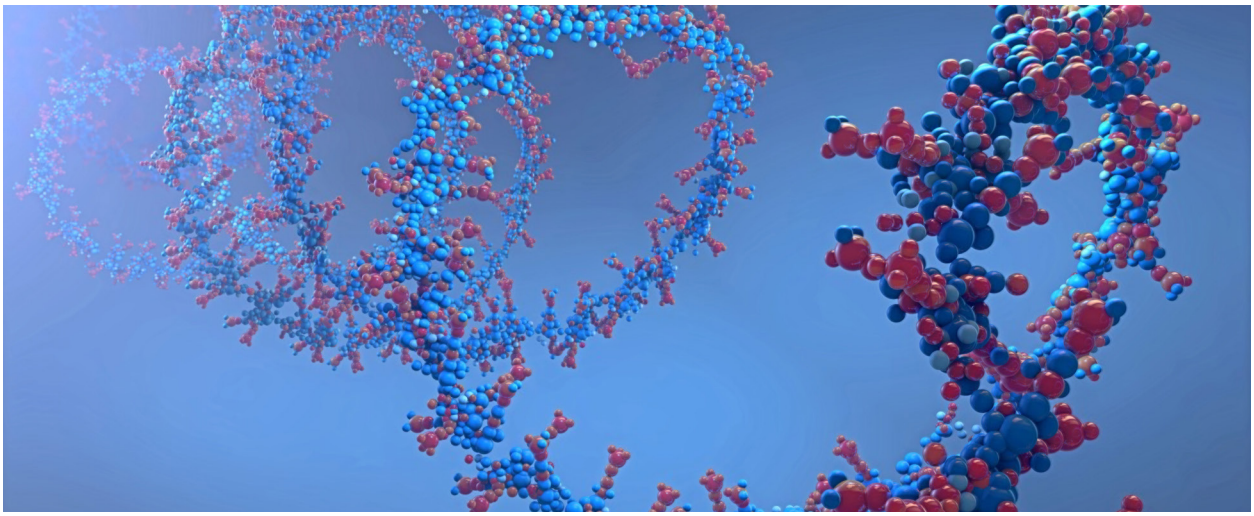
15. Total sales for the second quarter of 2021 consist of $7.838 billion from Pfizer and €5.266 billion ($6.239 billion) from BioNTech.

16. The BioNTech portion of guidance consists of estimated COVID-19 vaccine revenues for the 2021 financial year upon delivery of supply contracts of ~2.2 billion doses signed as of July 21, 2021. The dollar value of the ~€12.4 billion projected in Q1 by BioNTech fell during Q2 from $15.1 billion to $14.7 billion due to currency fluctuations.

Top 10 RNA-Based Biopharmas

Since 2018, COVID-19 vaccines propel revenues of public companies into the stratosphere, while funding for private companies grew much slower

Source: Christoph Burgstedt / iStock / Getty Images Plus



In GEN's *initial A-List published in 2018, the top five public companies generated a combined $1.536 billion in revenues for 2017 and the first three quarters of 2018. By contrast, the top five public companies appearing on this list generated a combined $31.218 billion in revenues in 2020 and the first three quarters of this year.*

In institutions and companies, investigators spent some two decades working on RNA-based drugs and vaccines before COVID-19 afforded many of them an opportunity to apply all that research into patients, with support from governments and regulators eager to fight the pandemic.

For two once obscure companies—Moderna, which went public in 2018, and BioNTech, which followed a year later—that opportunity has translated into multiple billions of dollars in new revenues. Not surprisingly as a result, both companies far outpace the other public companies ranked by *GEN* this year among top RNA-based biopharma companies.

Those companies and many others stand to make billions more from RNA-based vaccines and drugs. Only part of that is due to COVID-19 continuing to spawn a market for their messenger RNA (mRNA) vaccines and booster doses. The rest reflects expanding RNA-based pipelines by those companies and others, reflected recently in Moderna's dosing its first patient in a Phase III trial of its cytomegalovirus (CMV) vaccine.

A report issued last month by BCC Research projected the market for vaccines and therapeutics based on mRNA alone jumping from $46.7 billion this year—a figure that has already been surpassed by the two leading COVID-19 vaccines alone—to $101.3 billion by 2026, reflecting a compound annual growth rate (CAGR) of 16.8%.

Also standing to make potential billions are companies that have launched RNA-related collaborations during 2021. Just six days into the new year, Genentech, a member of the Roche Group, agreed to apply Ribometrix's discovery platform to discover, develop, and commercial-

ize small molecule drug candidates against RNA targets, through a collaboration that could generate more than $1 billion for the Durham, NC-based developer of RNA-based small molecule therapeutics.

Through November 12, Eli Lilly had launched two such collaborations with smaller RNA-focused partners. In May, Lilly committed up to $1.25 billion (including $25 million upfront) toward partnering with U.K.-based MiNA Therapeutics to develop small activating RNA (saRNA) drugs for up to five targets across Lilly's key therapeutic areas of cancer, diabetes, immunology, neurodegenerative diseases, and pain. Four months later, Lilly launched an up-to-$1.3 billion partnership ($50 million of that upfront) with ProQR to also pursue up to five targets by developing editing oligonucleotides using ProQR's Axiomer® RNA editing platform.

Below is *GEN's* updated A-List of top companies in RNA-based biotech, encompassing not only developers of vaccines and drugs based on various forms of RNA, but developers of RNA-based platform technologies.

This list includes the five largest public companies and five largest private companies. The public companies are ranked by their combined revenues for 2020 and 2021 (mostly the first through third quarters) as disclosed in regulatory filings, including sales of products or services, as well as revenue from collaborations and R&D activity.

Private companies are ranked by the total capital they have raised, as disclosed by the companies themselves, either in press statements or in responses to *GEN* queries verifying figures compiled by other sources. Companies that did not respond to those queries by deadline are listed with the highest figure published by an outside source.

Also included in this list are several "up and comers" that have either raised significant capital in recent months, shown positive data for their technologies, and/or launched significant new collaborations with partners.

Each company is listed with a summary of their recent activity.

To show how much the field has changed in three years: In *GEN's* initial A-List published in 2018, the top five public companies generated a combined $1.536 billion in revenues for 2017 and the first three quarters of 2018. By contrast, the top five public companies appearing on this list generated a combined $31.218 billion in revenues in 2020 and the first three quarters of this year.

A much slower jump in total capital has been seen among private companies, with the top five raising a combined $1.715 billion by 2018, and a combined $2.034 billion three years later.

Top Public Companies

#5. Sarepta Therapeutics

Revenue: $500.426 million in Q1-Q3 2021; $540.099 million in 2020

Sarepta Therapeutics has long focused on Duchenne muscular dystrophy, bringing to FDA approval three antisense oligonucleotides for patients amenable to skipping specific exons. The three—EXONDYS 51 (eteplirsen), VYONDYS 53 (golodirsen), and AMONDYS 45 (Casimersen)—generated strong revenue during the third quarter for Sarpeta, which raised its revenue guidance for 2021 by about $70 million, to between $605 million and $615 million. Also during Q3, Sarepta launched Part B of its MOMENTUM pivotal trial (SRP-5051-201; NCT04004065) for SRP-5051, the company's next-generation peptide-conjugated phosphorodiamidate morpholino oligomer (PPMO) for exon 51 skip-amenable Duchenne patients; and EMBARK (SRP-9001-301; NCT05096221), a pivotal trial for SRP-9001, Sarepta's micro-dystrophin gene therapy for Duchenne, being co-developed with Roche through an up-to-$2.85 billion collaboration. The three approved drugs are among 14 RNA programs within Sarepta's pipeline of 42 programs.

#4. Alnylam Pharmaceuticals

Revenue: $585.752 million in Q1-Q3 2021; $492.853 million in 2020

Alnylam founding CEO John Maraganore, PhD, in October announced plans to transition into an advisory board role at year's end, to be succeeded by President Yvonne Greenstreet, MBChB. His accomplishments included laying out several five-year plans (most recently Alnylam P^5x25), through which the company has delivered RNA-based medicines for rare and prevalent diseases. These include hereditary transthyretin-mediated (hATTR) amyloidosis with polyneuropathy, where Alnylam on October 27 reported positive topline 18-month results from the Phase III HELIOS-A trial (NCT03759379) assessing vutrisiran. The RNA interference (RNAi) therapeutic completed enrollment in August ahead of schedule in the Phase III

HELIOS-B trial (NCT04153149) for ATTR amyloidosis with cardiomyopathy. That indication also being pursued in the Phase III APOLLO-B study (NCT03997383) by Alnylam's patisiran, approved in 2018 as ONPATTRO® for polyneuropathy of hATTR amyloidosis in adults.

#3. Ionis Pharmaceuticals

Revenue: $370.450 million in Q1-Q3 2021; $729.3 million in 2020.

Ionis Pharmaceuticals during the third quarter expanded its late-stage pipeline to seven Phase III programs, and acknowledged that tofersen (licensed to Biogen) missed its primary endpoint in the Phase III VALOR trial (NCT02623699) in people with superoxide dismutase 1 (SOD1) amyotrophic lateral sclerosis (ALS), with Biogen evaluating next steps. But Biogen and Ionis added that tofersen showed signs of reduced disease progression across multiple secondary and exploratory measures that included motor function, respiratory function, and quality of life. In November, the company launched a second Phase III trial (CORE; NCT05079919) of its ligand-conjugated antisense (LICA) medicine olezarsen in people with severe hypertriglyceridemia. Ionis expanded its LICA medicine platform in July through technology licensed from Bicycle Therapeutics for $45 million upfront—including an $11 million equity investment in Bicycle.

#2. Moderna

Revenue: $11.260 billion in Q1-Q3 2021; $803.395 million in 2020

Moderna's shares tumbled 33% between November 3 and 12 on investor jitters over distribution delays for its COVID-19 vaccine, earnings that missed analyst forecasts, and ongoing patent disputes with the NIH and Arbutus Biopharma. Yet this past year, Moderna's COVID-19 vaccine (along with the Pfizer/BioNTech shot) showed how successfully RNA-based biopharmas can disrupt the industry. Moderna's revenues have multiplied exponentially from $60.209 million in 2019 and $803.395 million in 2020 (about two-thirds consisting of grant funding from the federal Biomedical Advanced Research and Development Authority). Moderna's mRNA clinical pipeline consists of 37 programs in development across 34 development candidates, including 21 in ongoing clinical studies. In October, Moderna's six-RNA vaccine mRNA-1647 became only the company's second candidate (and first besides the COVID-19 vaccine) to advance into a Phase III trial (NCT05085366) dubbed "CMVictory."

#1. BioNTech (made 2018 list as a private company)

Revenue: €13.444 billion ($15.384 billion) in Q1-Q3 2021; €482.325 million ($551.905 million) in 2020

"The last 18 months have demonstrated the power flexibility and the speed of our mRNA vaccine technology," BioNTech CEO and co-founder Ugur Sahin told analysts November 10. Like Moderna, BioNTech's revenues have zoomed with development of a COVID-19 vaccine. As of November 2, BioNTech and partner Pfizer delivered 2 billion-plus doses of BNT162b2, one of 22 mRNA candidates among 30 programs disclosed in the company's pipeline. The COVID-19 vaccine accounted for 99% of BioNTech's €6,087.3 billion ($6.966 billion) in Q3 revenues, with the company raising its 2021 revenue forecast for the shot from €15.9 billion ($18.2 billion) to between €16 billion and €17 billion ($18.3 billion and about $19.5 billion). BioNTech's RNA success has extended into oncology with a Phase II trial of autogene cevumeran (BNT122/RO7198457), under study in colorectal cancer and other solid tumor indications, partnered with Genentech, a member of the Roche Group.

Top 5 Private Companies

#5 Nutcracker Therapeutics

Total Capital Raised: $219.437 million X

While Nutcracker Therapeutics has been quiet since announcing a $60 million Series B financing last year, the company almost as quietly informed the U.S. Securities and Exchange Commission on September 3 that it raised $144.5 million--$144,499,977, to be precise—toward a planned financing of $200 million ($199,999,994). Nutcracker develops RNA therapeutics through a microfluidic, biochip-based platform it formally and aptly calls ACORN, and informally calls "GMP-in-a-box." ACORN is a computer-controlled RNA manufacturing system that starts with a nucleic acid sequence of interest and produces optimized nanoparticle-encapsulated RNA therapeutics on dedicated, single-use biochips. According to Nutcracker, all steps are performed in an automated, fully isolated microfluidic path, enabling rapidly scalable, efficient manufacturing of high-quality products within smaller footprint facilities with reduced operating costs compared to conventional bioreactor manufacturing.

- X Figure compiled by adding up the sums of four financings disclosed by the company, either via announcement or in filings with the U.S. Securities and Exchange Commission. These include $4 million

in seed financing (May 17, 2018), a $10.9 million Series A round (March 21, 2019), a $60 million Series B announced by the company (September 23, 2020), and an additional $144.5 million (September 3, 2021).

#4. Deep Genomics

Total Capital Raised: $236.7 million

Deep Genomics says its efforts to develop "programmable" RNA therapeutics based on its artificial intelligence discovery platform were expanded when it completed a $180 million Series C financing led by SoftBank Vision Fund 2* in July. The company focuses on applying AI and machine learning to program and prioritize "transformational" RNA therapeutics for genetic diseases. Deep Genomics' pipeline consists of preclinical candidates for four CNS conditions—Parkinson's disease, pediatric epilepsy, Niemann-Pick Disease Type C, and frontotemporal dementia—and two metabolic disorders, Wilson disease and refractory gout. The company also has four undisclosed preclinical programs partnered with BioMarin Pharmaceutical under a collaboration of undisclosed value. That collaboration gave BioMarin an exclusive option to obtain Deep Genomics' development and commercialization rights to each program.

#3. Sirnaomics

Total Capital Raised: $270 million

Sirnaomics has racked up a pair of $105 million financings over the past 13 months—a Series D round completed in October 2020, and a Series E round completed in July. The company said proceeds from the Series E will fund the continued development of its novel RNAi therapeutics for treating human disorders as diverse as cancers, viral infections, fibrosis, and metabolic diseases. The capital is also going toward developing its delivery technology platforms and expanding its large-scale manufacturing capacity to support its pipeline at different clinical stages. That pipeline is led by STP705 and STP707, which are in clinical phases for 12 indications encompassing cancer and fibrosis. Sirnaomics is headquartered in Gaithersburg, MD, with subsidiaries in Suzhou and Guangzhou, China.

#2. Laronde

Total Capital Raised: $490 million

Laronde is French for "the round," which explains its approach to engineering a new class of RNA that is circular rather than linear. Laronde's Endless RNA™ (eRNA) is a versatile synthetic RNA platform designed to instruct cells to express a desired therapeutic protein inside the body. Because eRNA has no free ends, it is not recognized by the immune system and is stable, enabling a longer duration of protein expression than linear RNA. "We're talking about weeks to months," Laronde CEO Diego Miralles, MD, told GEN Edge in September. In August, Laronde completed $440 million in Series B financing led by Flagship Pioneering, which launched the company in 2017 and brought it out of stealth mode in May of this year, committing $50 million to the startup.

#1. Abogen Biosciences

Total Capital Raised: $817.5 million X

Abogen flabbergasted analysts and other observers of the RNA therapeutic space in August, when the mRNA-based biotech announced that it completed an eye-popping "more than $700 million" Series C financing with participation mostly from Asian-based investment firms, as well as Eli Lilly's Lilly Asian Ventures. Suzhou-based Abogen said it intended to use the capital toward developing the mRNA vaccine candidate against COVID-19 it is co-developing with Chinese-based Walvax Biotechnology; advancing more vaccine and oncology programs into the clinic; and reinforcing Abogen's "leading position" as an mRNA therapy in China. Though less well known globally among Chinese COVID-19 vaccine developers as Sinovac (CoronaVac) and Sinopharm Group (BBIBP-CorV and a second candidate), Abogen in April advanced its shot against the virus into a Phase III trial (NCT04847102).

Companies to Watch

Arrowhead Pharmaceuticals

Arrowhead Pharmaceuticals develops RNA interference (RNAi) therapies through its Targeted RNAi Molecule (TRiMTM) platform. Revenues were $100.004 million for the nine months ending June 30, and $87.992 million in the fiscal year ending September 30, 2020. On November 15, Arrowhead presented Phase I/II (NCT04720534) data showing ARO-APOC3, which targets apolipoprotein C-III (APOC3), "may represent a promising RNAi therapeutic for the treatment of [severe hypertriglyceridemia] sHTG with infrequent dosing of every 3 months or every 6 months." Collaboration partner Janssen Pharmaceuticals shared Phase II trial (NCT03982186) data showing the highest 200 mg dose of small interfering RNA (siRNA) therapeutic JNJ-3989 (formerly ARO-HBV) led to 74.7% of patients achieving <100 IU/mL of Hepatitis B surface antibody (HBsAg). In June, Arrowhead licensed ARO-XDH for uncontrolled

gout to Horizon Therapeutics through a collaboration that could generate up to $700 million ($40 million upfront) for Arrowhead.

Dicerna Pharmaceuticals

Dicerna Pharmaceuticals—soon to be acquired by Novo Nordisk for $3.3 billion—just missed being ranked among top public companies, finishing with revenues of $151.894 million in Q1-Q3 2021 and $164.307 million in 2020. On November 12, Dicerna declared proof of principle for the first two targets in a potentially $3.7 billion-plus collaboration with Eli Lilly launched in 2018 to develop new treatments based on 10+ targets in cardio-metabolic disease, neurodegeneration, and pain. In September, Dicerna dosed the first subjects in a Phase I trial (NCT05021640) assessing DCR-AUD, Dicerna's GalXC RNAi therapeutic candidate for the treatment of alcohol use disorder. A month earlier, Dicerna reported positive topline data from its pivotal PHYOX2 trial (NCT03847909) showing that nedosiran, its GalXC RNAi therapeutic candidate for primary hyperoxaluria, showed statistically significant reduction from baseline in urinary oxalate (Uox) excretion compared to placebo.

Locanabio

Locanabio uses gene therapy to deliver RNA binding protein-based systems designed to correct the RNA "message" in severe neurodegenerative, neuromuscular and retinal diseases. In May, Locanabio presented positive preclinical *in vivo* results at the 24th Annual American Society of Gene and Cell Therapy (ASGCT) Meeting showing a novel PUF RNA-binding protein system delivered via an adeno-associated virus serotype 9 (AAV9) vector was safe and effective in eliminating toxic CUG repeats in a mouse model of myotonic dystrophy type 1 (DM1). In addition to DM1, Locanabio's pipeline includes candidates for Huntington's disease, Spinocerebellar ataxia type 1, Amyotrophic Lateral Sclerosis (ALS targeting the C9orf72 gene), frontotemporal dementia, and retinal disease. Locanabio has raised $159 million in total capital, most of that from a $100 million Series B round in December 2020.

ProQR

ProQR landed a big-pharma partner in September when Eli Lilly began collaborating with the Dutch company to discover, develop, and commercialize RNA therapies for genetic disorders in the liver and nervous system, based on ProQR's Axiomer® RNA editing platform. The collaboration generated $50 million upfront for ProQR and could yield up to $1.25 billion in research, development, and commercialization milestone payments, plus royalties. "There's significant room beyond that to potentially do additional partnerships," ProQR Founder and CEO Daniel A. de Boer told GEN. Axiomer is designed to enable the editing of single nucleotides in RNA in a highly targeted and specific manner based on editing oligonucleotides (EONs) designed to recruit endogenous Adenosine Deaminases Acting on RNA (ADAR) enzymes to a selected target adenosine in a disease-associated RNA.

Shape Therapeutics (Shape^{TX})

Shape Therapeutics (Shape^{TX}) launched an up-to-$3 billion collaboration with Roche in August to apply its RNA editing platform RNAfix™ and potentially leverage its AAVid™ technology platform for next-generation tissue-specific AAVs to develop gene therapies against Alzheimer's disease, Parkinson's disease, and rare diseases. The company's pipeline targets 52 genes implicated in these diseases and others, including Rett Syndrome, Stargardt disease, Alpha-1 antitrypsin deficiency (AATD), and Duchenne muscular dystrophy, and cystic fibrosis. Shape^{TX}'s suite of tech platforms broadly enable RNA targeting, RNA editing, and RNA replacement for patients suffering from genetic disorders with high unmet need. Seattle-based Shape^{TX} completed a $112 million Series B financing in July, saying the proceeds would enable it to continue building its RNA tech portfolio and accelerate development through partnerships.

Stoke Therapeutics

Stoke Therapeutics gives new meaning to the phrase, "it takes two to tango,"--as in Targeted Augmentation of Nuclear Gene Output (TANGO). The research platform has generated antisense oligonucleotides that bind to pre-mRNA, helping the target genes produce more protein. By selectively restoring protein levels, Stoke reasons it can treat a broad range of diseases where patients have one healthy copy of a gene and one mutated copy that fails to produce an essential protein. On November 8, Stoke nominated a second clinical candidate, STK-002, to treat autosomal dominant optic atrophy (ADOA). Earlier this year Stoke reported positive interim data from its Phase I/IIa MONARCH trial (NCT04442295) assessing its first clinical candidate, STK-001, in children and adolescents with Dravet syndrome. Of 11 patients in single ascending dose cohorts (10mg, 20mg, 30mg), eight showed a reduction in convulsive seizure frequency.

Top 10 Synthetic Biology Companies

Largest public and private companies (plus 8 up-and-comers) bask in the glow of growing interest in engineering organisms

Source: iStock/DeoSum

Investors pumped $4.6 billion into synthetic biology or "synbio" companies—more than four times the $904.7 million invested in the sector during Q1 2020, according to figures compiled by SynBioBeta, a community of engineers, investors, and other synbio stakeholders.

Any doubts about synthetic biology's attractiveness to investors were likely shattered during the first quarter, when investors pumped $4.6 billion into such companies—more than four times the $904.7 million invested in the sector during Q1 2020, according to figures compiled by SynBioBeta, a community of engineers, investors, and other synbio stakeholders.

"It's Silicon Valley investing in the next big thing, and the next exciting thing, and paying it forward to the next generation of entrepreneurs," John Cumbers, SynBioBeta's founder, explained during a recent *GEN Live* focused on synthetic biology's growth and challenges (Download the episode here).

While synthetic biology has applications that include flavors, food, fragrances, and numerous things not beginning with the letter "f," it was life sciences companies that led the synbio financing rush during Q1, according to a SynBioBeta report. ElevateBio scored the quarter's largest financing with a $525 million Series C round intended to support the acceleration and scaling of ElevateBio's end-to-end cell and gene therapy technology platform offering.

Next-highest, raising $400 million in Series C capital, was Insitro, which uses machine learning and data generation at

scale to carry out drug discovery and development—in the process attracting two biopharma giants among its collaboration partners, Bristol-Myers Squibb and Gilead Sciences.

Looking beyond this year, synbio is expected to more than triple in size as an industry from $9.5 billion this year to $30.7 billion, according to a MarketsandMarkets report released in May—a compound annual growth rate of 26.5%.

Below is *GEN*'s first-ever A-List for synthetic biology—the five largest public companies and five largest private companies. The public companies are ranked by their 2020 revenues as disclosed in regulatory filings, including sales of products or services, as well as revenue from collaborations and R&D activity. Private companies are ranked by the total capital they have raised, as disclosed by the companies themselves, either in press statements or in responses to *GEN* queries verifying figures compiled by other sources.

Also included in this list are several "up and comers" that have either raised significant capital in recent months, shown positive data for their technologies, and/or launched significant new collaborations with partners.

Each company is listed with a short explanation of their recent activity.

Top Public Companies

#5. Codexis

Revenue: $69.056 million in 2020; $18.032 million in Q1 2021

Codexis on June 17 raised its 2021 investor guidance after receiving a binding purchase order from an undisclosed global pharma for up to $13.9 million of a proprietary "high-performance" enzyme. Total revenues are expected to range between $89 million and $93 million, up from $82 million to $85 million. Codexis has also increased its product revenue guidance to between $45 million and $48 million, up from $36 million to $39 million. Codexis signaled its commitment to synthetic biology in November 2020 by announcing the SynBio Innovation Accelerator collaboration with Casdin Capital. The Accelerator aims to fund early-stage companies with disruptive technology platforms or unique product development capabilities in synthetic and industrial biotechnology. Codexis' first Accelerator investment was made in Arzeda, a privately-held computational protein design company.

#4. Ginkgo Bioworks

Revenue: $77 million in 2020

Ginkgo Bioworks took on additional financial muscle by agreeing to go public in May through a $17.5 billion merger with a special purpose acquisition company (SPAC) that is expected to provide up to $2.5 billion of gross cash proceeds. The SPAC merger with Soaring Eagle Acquisition Corp. implies a pre-money equity valuation of $15 billion for Ginkgo, launched in 2008 by co-founders who have worked together for close to 20 years since meeting at MIT. Their goal was to develop a platform that could program cells as easily as computers across applications that include food, agriculture, pharmaceuticals, and industrial chemicals. In June, Ginkgo agreed to apply its organism engineering expertise to an unidentified Sumitomo Chemical bio-based commercial product and explore bio-based production methods that can replace petroleum-based products.

#3. Twist Bioscience

Revenue: $90.1 million in fiscal year ending September 30, 2020; $59.364 million in October 2020–March 2021

Twist Bioscience, whose disruptive platform manufactures synthetic DNA by "writing" DNA on a silicon chip, joined Illumina, Microsoft, and data storage giant Western Digital last year to co-lead the DNA Data Storage Alliance they established with 11 partner tech-based companies and institutions. The alliance aims to advance DNA data storage by agreeing upon a "roadmap" of definitions and standards to help the industry achieve interoperability between solutions. In June, Twist acquired iGenomX, which offers multiplex library preparation tools for next-generation sequencing (NGS) workflows; and partnered with Regeneron Genetics Center to produce a custom NGS population genetics genotyping assay designed to incorporate genetic differences of global populations, thus gaining insights into disease mechanisms, identifying novel drug targets, and accelerating drug discovery and development.

#2. Precigen

Revenue: $103.178 million in 2020; $24.511 million in Q1 2021

Precigen's wholly-owned subsidiary Precigen ActoBio on June 10 reported positive topline results from a

Phase Ib/IIa trial (NCT03751007) assessing its microbe-based therapeutic AG019—developed through the company's ActoBiotics™ platform—in recent-onset type 1 diabetes. Following an eight-week treatment cycle of oral AG019 alone, 5 of 9 adults (56%) showed stabilization or increase of C-peptide levels during the first six months—as did 7 of 10 adults (70%) and all four adolescents treated with AG019 and teplizumab. Earlier this year, Precigen launched a first-in-human Phase I trial (NCT04724980) PRGN-2012, the company's first off-the-shelf AdenoVerse™ immunotherapy targeting infectious disease. Trials are also in progress for PRGN-2009 in HPV-associated cancers, as well as the Ultra-CAR-T® trials evaluating PRGN-3005 in ovarian cancer and PRGN-3006 in acute myeloid leukemia.

#1. Amyris

Revenue: $173.137 million in 2020; $176.859 million in Q1 2021

Amyris, which produces sustainable ingredients for the Clean Health & Beauty and Flavors & Fragrances (F&F) markets, has also developed a COVID-19 vaccine with the Infectious Disease Research Institute. On July 1, Amyris licensed the vaccine to Nant Africa through an agreement "expected to generate several million dollars in near term upfront and milestone payments" for the company, plus long-term royalties. Amyris Q1 revenue surpassed all of 2020's; President and CEO John Melo credited continued product-related revenue growth and completion of the company's second strategic ingredients transaction, a potentially more-than-$500 million supply/manufacturing agreement inked in March with DSM Nutritional Products, a subsidiary of Royal DSM to supply Amyris's product portfolio of F&F ingredients. That deal alone added $144 million to Amyris' quarterly revenue total.

Top Private Companies

#5. Apeel Sciences

Total Capital Raised: $390.1 million[1]

Not many companies can brag about having Oprah Winfrey and Katy Perry among their investors, but Apeel Sciences can. Based in Goleta, CA, Apeel manufactures plant-derived coatings used by fresh food growers, suppliers, and retailers to keep produce fresh—and thus curb global food waste. Apeel's approach to innovation made it one of 61 companies designated 2018 World Economic Forum Technology Pioneers, and landed it on TIME magazine's Best Inventions 2019 and Fast Company's World Changing Ideas 2019 lists. Apeel completed its most recent financing, a $250 million Series D round, in May 2020, which brought the company's valuation to over $1 billion, after raising $70 million in Series C (2018), and lesser amounts in earlier rounds and seed stage financings.

[1]Apeel referred *GEN* to the $390.1 million "total funding amount" figure compiled by the venture capital market data tracker Crunchbase.

#4. Insitro

Total Capital Raised: $643 million

More than half of Insitro's total capital raised came through a single financing, the $400 million Series C round completed in March and led by Canada Pension Plan Investment Board (CPP Investments). The financing capped a busy but productive 12 months during which the company launched an up-to-$2 billion-plus collaboration with Bristol Myers Squibb to discover and develop novel therapies for amyotrophic lateral sclerosis and frontotemporal dementia; built and demonstrated its target discovery platform in a NASH collaboration with Gilead Sciences, for which Insitro received its first operational milestone payment; and acquired Haystack Sciences, aiming to strengthen its machine-learning enabled drug discovery efforts. Earlier, Insitro raised $143 million in Series B capital (May 2020) and $100 million in Series A (2018).

#3. ElevateBio

Total Capital Raised: $869.3 million

ElevateBio in March completed a hefty $525 million Series C financing, with plans to use the proceeds toward developing and expanding its technology platforms, growing its process development and GMP manufacturing capacity, advancing industry partnerships, and developing drug candidates. Based in Cambridge, MA, ElevateBio creates and operates a portfolio of companies across platforms that include gene editing, induced pluripotent stem cells, and protein, viral, and cellular engineering. A recent job ad sought an associate scientist who can, among other skills, "apply recent advances in synthetic biology to create and characterize the next generation of CARs/TCRs." ElevateBio completed a $150 million Series A financing in May 2019 upon its launch, followed by a Series B that closed last year at $193 million.

#2. National Resilience (Resilience)

Total Capital Raised: Over $964 million

National Resilience (Resilience) describes itself as "the next generation of life sciences manufacturing." Resilience defines next-gen to include synbio, as it listed "synthetic biology experimental approaches" among preferred experience sought for a recent job opening, vp/head of platform R&D. Resilience plans to modernize and expand the production capacity of its Ontario-based subsidiary Resilience Biotechnologies using C$199.2 ($164 million) from the government of Canada's Strategic Innovation Fund awarded in May. A month earlier, Resilience acquired privately-held Ology Bioservices, an Alachua, FL, biomanufacturer, for an undisclosed price, adding 300 staffers and expertise developing and manufacturing drugs and biologics for commercial customers and the U.S. government. Resilience previously acknowledged having raised "over $800 million" in private capital, most of that being the eye-popping $750 million Series B financing completed in November 2020.

#1. Impossible Foods

Total Capital Raised: More than $1.5 billion

Nearly a year after raising $200 million in Series G financing, bringing its total capital raised to "more than $1.5 billion," plant-based meat company Impossible Foods remains hungry for growth. The company spent the first six months of the COVID-19 pandemic accelerating the rollout of its Impossible™ Burger from 150 to more than 8,000 grocery stores nationwide, including national chains such as Kroger, Trader Joes, and Walmart. Impossible Burgers can also be found at Burger King, Red Robin, and White Castle. Behind the meatless meat-like taste is heme, a plant-based molecule produced by fermentation of genetically engineered yeast to which DNA from soy plants are inserted. Long-term, Impossible Foods plans to create plant-based versions of every major category of animal-derived food products.

Up & Comers

Antheia

Privately-held Antheia closed an oversubscribed $73 million Series B financing June 30, bringing its total capital raised to $98 million. Proceeds are intended to support commercialization of Antheia's first pharmaceutical compound, and production scale-up for several critical active pharmaceutical ingredients and key starting materials. Using bio-based fermentation, Antheia produced several classes of plant-inspired pharmaceuticals it said cannot be manufactured through conventional scalable synthetic chemistry. The company has produced its first molecule, a key starting material for several medicines, at "commercially relevant" titers at pilot scale (300 L), showing chemical equivalence to material extracted from plants. In September 2020, Antheia co-founder and CEO Christina Smolke, PhD, described in *Nature* the first successful microbial biosynthesis of tropane alkaloids, used for treating neuromuscular disorders.

Beam Therapeutics

Beam Therapeutics is combining its base editing technology with Apellis Pharmaceuticals' complement expertise to co-develop six research programs focused on C3 and other targets in the eye, liver, and brain. The collaboration, announced June 30, brings Beam $75 million in upfront cash and near-term milestones. Beam said in May it was on track to submit its first IND application for BEAM-101 (in development for sickle cell disease and beta thalassemia) and begin IND-enabling studies for BEAM-102 (sickle cell disease) and BEAM-201 (T-cell acute lymphoblastic leukemia), plus nominate its first development candidate from its portfolio of liver disease programs. Earlier this year, Beam acquired Guide Therapeutics for up to $440 million, integrating Guide's in vivo lipid nanoparticle screening platform and library of lipids and lipid formulations.

Berkeley Lights

Berkeley Lights just missed being ranked among *GEN's* top 5 public synbio companies after finishing 2020 with $64.303 million in revenue. The developer of a tech platform designed to enable rapid functional characterization of single cells at scale nearly tripled its cash and cash equivalents last year, to $233.408 million, a figure that dipped 1% in Q1, to $230.165 million. Much of that cash windfall reflected the $187.9 million in aggregate net proceeds that Berkeley Lights raised from an IPO launched in July 2020. Synthetic biology is one of Berkeley's four markets (the others are antibody therapeutics, cell therapy, and gene therapy), accounting for nearly 11% ($1.984 million) of Berkeley Lights' Q1 revenue and 12% ($8 million) of 2020 revenue.

Codex DNA

Codex DNA closed its IPO on June 22, generating approximately $122.7 million in aggregate gross proceeds through the sale of 7,666,664 shares of common stock at $16 per share, including the full exercise of the underwriters' option to purchase up to 999,999 additional shares at the IPO price. The company's products aim to enable researchers to rapidly, accurately, and reproducibly build or "write" high-quality synthetic DNA and mRNA that is ready to use in many downstream markets. Codex DNA markets the BioXp™ system, a fully automated benchtop end-to-end automated workstation designed to provide a turnkey, end-to-end solution for generating synthetic DNA and mRNA starting from DNA sequence. The company's gene synthesis portfolio also includes BioXp™ biofoundry services, Gibson Assembly® reagents, and Vmax™ chemically competent cells.

Sana Biotechnology

Sana says it is building capabilities enabling high throughput cell engineering and gene editing and control through technologies that include synthetic biology. The preclinical-stage developer of in vivo and ex vivo cell engineering platforms—aimed at revolutionizing treatment across numerous therapeutic areas—has advertised recently for a principal scientist, synthetic biology. Sana's cash, cash equivalents, and marketable securities more than doubled during Q1, to $981.9 million as of March 31, following an IPO in February that generated net proceeds of $626.4 million. Most recently on June 26, Sana presented data showing survival of transplanted stem cells without immunosuppression in non-human primates. The transplanted cells were induced pluripotent stem cells engineered with Sana's hypoimmune gene modifications designed to enable immune evasion.

Synlogic

Synlogic saw its share price plunge 25%, to $1.81 in June 2020 after announcing the end of a collaboration launched in 2016 to develop Synthetic Biotic medicines with AbbVie to treat inflammatory bowel disease. Since then, Synlogic's shares have more than doubled, to $4.01 on June 29, following more positive news about other Synthetic Biotic candidates. At the American Association for Cancer Research virtual annual meeting in April, Synlogic presented data on its solid tumors and lymphoma immunotherapy drug SYNB1891 from a Phase I trial (NCT04167137). A month earlier, Synlogic said another Synthetic Biotic, SYNB8802, achieved proof of concept mechanism in a Dietary Hyperoxaluria study where healthy volunteers on a high oxalate and low calcium diet were treated with multiple ascending doses of the drug.

Synthego

Synthego, which has raised "over $250 million" in total capital, says its position as a key accelerator of therapeutic development from early research through clinical trials was reinforced in May when it obtained ISO 9001:2015 certification based on an independent audit of its entire manufacturing process for GMP-grade single-guide RNA (sgRNA), used by biopharma customers for R&D of gene therapeutics and CRISPR-based gene editing. As *GEN* reported in May, Synthego has ridden the single-cell analysis trend in CRISPR screening, applying machine learning and automation to handle the massive data output from these types of experiments. In April, Synthego launched Eclipse™, a new high-throughput cell engineering platform designed to accelerate drug discovery and validation by providing highly predictable CRISPR-engineered cells at scale through the integration of engineering, bioinformatics, and proprietary science.

Zymergen

Zymergen raised approximately $530 million in net proceeds in April—more than four times its $121.035 million in cash and cash equivalents as of March 31—through an IPO with full exercise by underwriters of their option to purchase additional shares. The IPO followed nearly $1 billion in past private financings by Zymergen, which sums up its innovative manufacturing approach as "biofacturing," declaring: "We Make Tomorrow." Zymergen's approach integrates molecular biology, chemistry, materials science, lab automation systems, software applications, unique databases, and machine learning algorithms in order to launch products in about half the time and a tenth of the cost incurred by traditional chemical and materials companies. In May, Zymergen appointed Aindrea Campbell, formerly of Apple and Ford, to oversee global manufacturing and supply chain activities.

Top 10 U.S. Biopharma Clusters

Pandemic reshuffles the bottom of *GEN's* regional rankings but not the top, for now

Source: National Resilience Inc. via Business Wire

Sanofi recently sold its 310,000-square-foot Allston plant built by its Genzyme subsidiary to Resilience, a San Diego-based provider of biopharma manufacturing services, which has offered jobs to all 250 staffers and is planning to expand headcount. Boston and neighboring Cambridge, MA, anchor a regional biopharma cluster that retains its top ranking in GEN's Top-10 list despite signs of growing strength from its closest competing regions.

Charles Dickens' opening line of *A Tale of Two Cities*—"It was the best of times, it was the worst of times"—was evoked recently by the head of the nation's largest life sciences real estate owner to describe the past year for the industry served by his real estate investment trust.

"With respect to the industry, 2020 is the ultimate paradox: The worst year of our lives, yet the greatest year ever for the life science industry," Joel S. Marcus, Alexandria Real Estate Equities' executive chairman and founder, told analysts February 2 after releasing fourth-quarter and full-year 2020 results. "[There's] much work to do to rebuild businesses and lives so devastatingly impacted, and I would say, it's going to take a good part of this decade to do that for many people who've been really so devastated."

Yet the industry scramble to develop vaccines and drugs against COVID-19 and diagnostics for the virus also propelled the life sciences to record high venture capital of $23.5 billion in 626 deals in eight life sciences categories

covered by *GEN* (biotechnology, disease diagnosis, drug delivery, drug development, drug discovery, drug manufacturing, pharmaceutical distribution and wholesale, and pharmaceuticals/drugs), according to the PwC/CB Insights quarterly MoneyTree™ Report. PitchBook and the National Venture Capital Association recorded even more activity in the "biotech and pharma" category of $27.4 billion last year, up from $17.3 billion in 2019.

Judging from the numbers reported by the nation's top U.S. clusters, 2020 saw record-high amounts of lab space and NIH funding, as well as record-high numbers of jobs and patents. Those highs are reflected in high regional numbers seen in *GEN's* annual ranking of the nation's top 10 biopharma clusters. *GEN* ranks regions based on five quantifiable criteria:

- **NIH funding**—Taken from the publicly available NIH RePORT database, for the current federal fiscal year through March 1, plus all of fiscal year 2020, which ran from October 1, 2019, through September 30, 2020.
- **Venture capital (VC) funding**—Figures for all of 2019 and all of 2020. For some regions, figures were compiled through the publicly available PwC/CB Insights MoneyTree™ Report. For other regions where figures were not available from MoneyTree, figures were furnished to *GEN* by regional life sciences groups.
- **Patents**—Based on the number of patents containing the word "biotechnology" awarded since 1976 in namesake cities and suburbs where key companies are located.
- **Lab space**—Based on the highest total-size-of-market figure, in millions of square feet, furnished by any of several commercial real estate companies, including JLL (in its annual U.S. Life Sciences Outlook report for 2020), CBRE, Cushman & Wakefield, and Newmark.
- **Jobs**—Based on figures furnished by regional life sciences groups, or where those figures do not exist, from JLL's report. While job numbers are included in the rankings, less weight had to be given to job totals in regions where *GEN* has found widespread discrepancies in job figures.

This year's rankings show the leading regional cluster maintaining its number-one position which it has held since the 2015 A-List—a year after *GEN's* first top-10 list ranking U.S. regions. However, clusters 2–5 are nipping at its heels, and coming closer to the top than ever, thanks to playing on different strengths. Also since the 2019 A-List, the regions occupying positions #7 through #10 have all switched positions, with two regions gaining and two losing.

10. Chicagoland

Chicagoland ranks lowest in lab space, just 11th with 3.4 million square feet, but a series of planned developments is likely to improve that figure in coming years, starting with 423,454 square feet expected to open this year. That space is now being built by Trammel Crow at Fulton Labs, in Chicago's Fulton Market neighborhood. Trammel Crow is partnering with life sciences entrepreneur, John Flavin, to launch Portal Innovations, a platform to seed-fund and accelerate life sciences, medical technology, and bioinformatics ventures.

Also interested in nurturing startups is Illinois Gov. JB Pritzker, who in December joined the state Department of Commerce in January to announce the $9 million **Rebuild Illinois Wet Lab Capital Program**, with the aim of expanding access to lab space to incubators, corporations, university researchers, and start-ups. Recipients must match the state funding.

More recently on February 18, Chicago's Plan Commission approved the $3.8 billion first phase of a $7 billion, 100-acre mixed-use plan by local development group GRIT. That first phase includes the 500,000-square-foot Chicago ARC (Accelerate, Redesign, Collaborate) Innovation Building, designed entirely for a mix of life-sci users that include universities, healthcare providers, biopharmas, and startups in specialties that include precision medicine, big data, and artificial intelligence. ARC's co-developers include Israel's Sheba Medical Center. Another megaproject with life sciences space is "The 78," a $7 billion, 62-acre mixed-use campus on Chicago's South Loop by University of Illinois and Related Midwest.

In suburban Deerfield, IL, Horizon Therapeutics last year expanded into the former U.S. headquarters of Takeda Pharmaceutical, after buying the 70-acre site for $115 million. The Windy city and its suburbs rank highest in jobs, fifth with 87,918 according to iBio (Illinois Biotechnology Innovation Organization). The region ranks ninth in three other criteria: NIH funding (2,568 awards totaling $1.234 billion), patents (1,755), and VC funding ($989.57 million in 2019 and 2020).

9. Raleigh-Durham, NC (including Research Triangle Park, NC)

Regional life science stakeholders recently mourned the loss of Sam Taylor, who died February 21 of pancreatic cancer at age 64. Taylor founded the North Carolina Biosciences Organization (NCBIO), served as its president since 2006, and played a key role in growing life sciences statewide.

Happier news came March 4, with Biogen announcing a $200 million gene therapy manufacturing facility at Research Triangle Park, set to add 90 jobs to the company's 1,900-person RTP workforce. Many of the region's life sciences attractions and expansions have been gene and cell therapy facilities by Astellas Pharma-owned Audentes Therapeutics (Sanford, NC), bluebird bio (Durham), Novartis Gene Therapies (formerly AveXis; RTP), and Pfizer (Sanford), with manufacturing sites also planned by Eli Lilly (pharmaceuticals, RTP) and Grifols (blood plasma, Clayton, NC). In February, Durham-based Humacyte, whose Human Acellular Vessels (HAVs) apply bioengineered human tissue to treat diseases, went public last month at a market capitalization of $1.1 billion through via a SPAC (special purpose acquisition company), plus $175 million in PIPE (private investment in public equity) financing.

The region is losing a headquarters, as Raleigh-based contract research organization PRA Health Services is being acquired by Dublin-headquartered ICON for $12 billion. However, it may gain more jobs from United Therapeutics as it weighs whether to grow its U.S. manufacturing operations at RTP or in Maryland; the company considers RTP a co-headquarters site to Silver Spring, MD, where UT emerged in 1996.

Raleigh-Durham-RTP-Chapel Hill is fifth in NIH funding (2,803 awards totaling $2.308 billion), and eighth in lab space (11.4 million square feet according to JLL). But the region is 10th in patents (1,408), venture capital (approximately 70% of the state's $1.103 billion in 2019 and 2020, or $772.1 million, according to the state-funded North Carolina Biotechnology Center)—and for now, jobs (39,588, according to JLL, though the biotech center tallies more than 67,000 statewide).

8. Seattle

After years of being sustained by top-flight universities and institutions, Seattle's life sciences cluster has enjoyed good news lately from growing companies: Immune therapeutics developer Alpine Immune Sciences scored an up-to-$865 million collaboration with AbbVie last year, with plans later this year to launch a Phase II study of Alpine's lead candidate, ALPN-101 for adults with active lupus. Seattle-based Sana Biotechnology, whose treatments are based on its engineered cells, raised approximately $675.6 million in gross proceeds last month through an IPO, less than a year after completing a VC financing of more than $700 million.

Also going public recently is Silverback Therapeutics, which is applying its ImmunoTAC platform to develop tissue-targeted drugs for cancer chronic viral infections, and other diseases. Silverback which raised approximately $277.7 million in gross proceeds in December, capping a year in which it collected $85 million in a Series C financing and $78.5 million in a Series B.

Seattle finished 2020-2021 with approximately $2.9 billion in VC in 2019 and 2020, jumping three notches to a tie for fifth (with Greater Philadelphia) from eighth in 2019, when its best showing was sixth in patents. Seattle also improved in NIH funding (sixth with 1,894 awards totaling $1.732 billion), but dipped to seventh in patents (2,336). The region ranked lower in lab space (ninth with 11.25 million square feet, according to Cushman & Wakefield) and 11th in jobs (35,914 as of 2019, according to statewide industry group Life Science Washington, which is working on a 2020 figure to be published in May).

As for Seattle's institutions, The University of Washington last year opened its $230 million Hans Rosling Center for Population Health, which has set for itself the ambitious goal of preventing the next pandemic. The Gates Foundation footed $210 million of the building's cost, with another $15 million coming from Washington state.

7. Greater Philadelphia

The "City of Brotherly Love" and its suburbs emphasize their concentration of companies and institutions focused on cell and gene therapy (CGT), with good reason. As of 2020, Greater Philadelphia was home to 36 CGT companies, pioneering researchers, and a CGT workforce of approximately 4,900 that could grow by up to 11,274 in 10 years, according to a report by the Chamber of Commerce for Greater Philadelphia's regional CEO Council for Growth, the University City Science Center, and University City District's West Philadelphia Skills Initiative.

CGT growth helps explain why the region has > 1 million square feet of new lab space under construction. In Philadelphia, Brandywine Realty Trust is building the 14-acre, $3.5 billion Schuylkill Yards campus across from Amtrak's 30th Street Station. Also in Philly is One uCity Square, a $280 million, 400,000-square-foot 13-story lab-office building being developed by Wexford Science & Technology with University City Science Center and Ventas—one of four projects totaling 1.35 million square feet and $750 million taking shape at uCity Square.

In King of Prussia, PA, a former GlaxoSmithKline R&D site and adjacent parcels have been transformed into The Discovery Labs, whose three components comprise a "one-stop shop" for CGT development. MRA Group is bringing the 600,000-square-foot Spring House Innovation Park to life in Lower Gwynedd Township, while in Doylestown, PA, the Pennsylvania Biotechnology Center is constructing a $19 million, 15,000-square-foot lab building.

Greater Philadelphia ranks highest in both lab space (fifth with 23.37 million square feet, according to Colliers) and VC (tied for fifth with Seattle at about $2.9 billion, according to Dealforma—with $1.6 billion going to CGT companies, says Select Greater Philadelphia Council, a regional business attraction organization). The region places sixth in patents (5,148), and eighth in both NIH funding (2,991 awards totaling $1.48 billion), and jobs (69,565 according to JLL and Select Greater Philadelphia).

6. Los Angeles / Orange County, CA

The first day of Los Angeles' COVID-19 lockdown, March 16, 2020, was also the day David J. Whelan joined regional industry group BioscienceLA as CEO: "I could not think of a more exciting time to be leading the growth of a vibrant ecosystem that will create new opportunities for all," Whelan told ShoutoutLA in January.

BioscienceLA isn't the region's only life sciences champion. Last fall, the public-private Los Angeles Economic Development Corp. (LAEDC), statewide life sciences industry group Biocom, the Center for a Competitive Workforce, and the Office of "City of Angels" Mayor Eric Garcetti partnered to launch "WhyLALifeScience," an online database designed to promote the region's life sciences strengths.

The region has several research anchors ranging from Cedars-Sinai to The Lundquist Institute (TLI)—which on March 8 partnered with the Bill and Melinda Gates Foundation to out-license TLI intellectual property covering a synthetic lung surfactant formulation, to be developed for respiratory distress syndrome for premature infants in low- and middle-Income countries. Bolstering LA/Orange's funding base is Westlake Village Partners, which in December raised two new funds totaling $500 million.

Thousand Oaks, CA, remains home to the region's largest biopharma Amgen with 24,300 staffers as of December 31, 2020 (up 900 employees or 3.8% from a year earlier)—and is home to two HATCHspaces® life sciences sites developed with Chicago-based Singerman Real Estate, a 50,000-square-foot small molecule manufacturing facility purchased from Amgen in October, and a 120,000-square-foot space.

LA/Orange leads the nation in life sciences jobs with 173,503 in 2019, according to Biocom data released last year, though LAEDC placed the number at 195,000 in December. The region is seventh in both lab space (more than 12.8 million square feet, CBRE reported in October) and NIH funding (2,449 awards totaling $1.535 billion), and eighth in both patents (1,876) and VC ($1.425 billion for 2019 and 2020, according to BioscienceLA).

5. San Diego

San Diego's Pacific coastline is among reasons it calls itself "America's Finest City." And if IQHQ has its way, that ocean view would be enjoyed by life sciences users occupying five buildings totaling 1.3 million square feet planned by the developer for the Manchester Pacific Gateway site, 12 acres south of Broadway between Pacific Highway and Harbor Drive. IQHQ, led by former BioMed Realty CEO Alan Gold, purchased 8+ acres of the site from Manchester Financial Group in September for an undisclosed price toward development of its "Research and Development District (RaDD)."

Developers aren't the only ones thinking bigger: Maravai LifeSciences grossed $1.863 billion when it went public in November, capping a year that saw the company and its TriLink Biotechnologies move to expanded space within San Diego, with TriLink completing its cGMP space in January. MilliporeSigma in April revealed plans for a $110 million second viral vector facility in Carlsbad, CA. Other companies, however, have returned sizeable spaces to market for subleasing, including sequencing giant Illumina (75,000 square feet).

San Diego fared best in VC (third with $4.794 billion

in 2019 and 2020), helped by the $750 million Series B financing completed in November by La Jolla-based Resilience, a provider of biopharma manufacturing services that emerged from stealth mode with more than $800 million in capital.

The region anchored by the "Plymouth of the West" also ranked fourth in patents (5,973), thanks to its strong base of universities led by University of California, San Diego, and numerous research institutions. San Diego is sixth in lab space (23.3 million square feet, according to Newmark), but ranks lower in jobs (seventh with 71,626 according to JLL, though statewide life sciences industry group BIOCOM counted 68,063) and 10th in NIH funding (2,118 awards totaling $1.162 billion).

4. BioHealth Capital Region [Maryland/Virginia/Washington, D.C.]

Well before COVID-19 wreaked havoc on the world, the Maryland/Virginia/Washington, DC "BioHealth Capital Region (BHCR)" had the building blocks of a region well-positioned against infectious disease. Baltimore-based Johns Hopkins University received nearly half the region's total NIH basic research funding. In Gaithersburg, MD, COVID-19-focused vaccine developers with substantial operations include AstraZeneca, Emergent BioSolutions—and Novavax, whose expansion plans were announced during a visit by Maryland Gov. Larry Hogan (R).

Bethesda, MD, is home to the FDA and NIH—and its National Institute for Allergy and Infectious Disease, whose director is Anthony S. Fauci, MD. Northern Virginia will soon be home to Drugviu, developer of a real-world evidence and patient-reported outcomes platform for immunological research, which is moving from New York City. In Richmond, VA, Phlow won up to $812 million over 10 years from the Biomedical Advanced Research and Development Authority (BARDA) in May toward manufacturing generic COVID-19 therapeutics. BHCR companies racked up more than $5.8 billion in awards from BARDA toward COVID-19 vaccines and drugs.Ceres Nanosciences of Manassas, VA, plans to add 50 jobs by increasing its manufacturing capacity for COVID-19 testing, Virginia Gov. Ralph Northam said March 3. Gene therapy developer Vigene Biosciences said it will more than triple its 125-person staff by adding 245 employees as it doubles its manufacturing footprint in Rockville, MD, where the company last year opened its HQ, R&D, and manufacturing sites. BHCR is 60% toward its goal of becoming a top-three cluster by 2023. The region is already third in NIH funding (4,051 awards totaling just over $3 billion), patents (6,015) and lab space (29.7 million square feet, according to JLL)—with almost 3 million new square feet under development or planned. The region places sixth in jobs (74,542 as of March, according to JLL), and seventh in venture capital ($1.677 billion, according to Crunchbase, GlobalData, and JLL).

3. New York / New Jersey

New York City enjoys a growing pipeline of life sciences development projects, with 1.1 million square feet to be built through 2021, on top of some 850,000 square feet completed since early 2019, according to CBRE.

Projects include Deerfield Management's $635 million conversion of 345 Park Avenue South into the approximately 300,000-square-foot "Cure" lab-space building, while Taconic Partners and Nuveen Real Estate in October announced plans to convert 125 West End Avenue into a 400,000-square-foot life sciences building. By 2022, Alexandria Real Estate Equities is set to complete a 550,000-square-foot third building at its Alexandria Center for Life Science on Manhattan's East Side, expanding the campus to 1.3 million square feet, while in December it completed 17,716 square feet across the East River in Long Island City. The Icahn School of Medicine at Mount Sinai, inked a 165,000-square-foot lease March 5 at The Georgetown Co.'s 787 11th Avenue, redeveloped for lab use on Manhattan's West Side. Across the Hudson River, public-private New Jersey Economic Development Authority (NJEDA) has facilitated large-scale redevelopment projects by creating the Brownfields Loan Program, designed to issue low-interest loans of up to $5 million toward assessment, investigation, and demolition. Also in the Garden State, Morris Plains, NJ-based Immunomedics was acquired by Gilead Sciences for approximately $21 billion, in a deal completed in October. In New York's Westchester County, Regeneron Pharmaceuticals has proposed adding 200,000 square feet of lab space to its Tarrytown, NY, headquarters campus. Biosciences is one of four "key" sectors to which Westchester has committed to growing through its new economic plan, announced March 8 by county director of economic development Brigitte Gibbons.

New York/New Jersey is second in both jobs (152,162 according to JLL) and NIH funding (6,164 awards totaling $3.308 billion). The region ranks fourth in both lab space (24.7 million square feet, according to JLL) and VC ($3.773 billion), and places fifth in patents (5,332).

2. San Francisco Bay Area

A recent newspaper article detailed how COVID-19 reshaped San Francisco, as reflected in new uses for the streets of "The City." The pandemic also brought new life to the Bay Area, helping it come closer than ever to recapturing the top spot that it held in *GEN's* first U.S. cluster list in 2014.

The Bay Area improved in four of the five criteria since *GEN's* last list in 2019, climbing from fourth to third in jobs (145,235, according to statewide life sciences industry group BIOCOM), and from third to second in lab space (33.1 million square feet, according to Cushman & Wakefield). San Francisco and suburbs lead the nation in patents (12,777) and VC ($10.749 billion in 2019 and 2020), while the Bay Area remained fourth in NIH funding (4,748 awards totaling $2.474 billion). The largest VC award was the $493 million Series C completed in April 2020 by Lyell Immunopharma, a developer of cell-based immunotherapies for any cancer, with a focus on CAR-Ts and solid tumors. Genentech, a member of the Roche Group, won approval from the City Council of South San Francisco, CA, in November for a near-doubling of space at its headquarters campus at One DNA Way, to 9 million square feet from 4.7 million. That could enable up to 12,550 more employees in addition to the roughly 10,000 based there in 2020.

Several of the region's companies found buyers willing to pay billions for them: Nestlé Health Science shelled out about $2.6 billion for Brisbane, CA-based Aimmune Therapeutics, developer of an FDA-approved children's peanut allergy treatment, while Alexion Pharmaceuticals snapped up South SF-based Portola Pharmaceuticals for $1.4 billion. However, Menlo Park, CA-based cancer liquid biopsy developer GRAIL's planned $8 billion purchase by Illumina is still in the works and set to close this year.

1. Boston / Cambridge, MA

Boston/Cambridge remains the nation's top biopharma cluster, thanks to number-one rankings in NIH funding (6,552 awards totaling $3.711 billion), reflecting its critical mass of world-class universities and research institutions; and lab space (35.2 million square feet, according to CBRE), reflecting a wave of corporate activity.

The region is second in patents (9,099) and VC ($10.113 billion in 2019 and 2020)—though Massachusetts finished 2020 with a record-high $5.8 billion, according to a report released March 4 by the Massachusetts Biotechnology Council (MassBio). Winning the state's largest VC award was Boston-based Atea Pharmaceuticals, which garnered $215 million in Series D financing in May and is partnering with Roche to develop COVID-19 antiviral candidate AT-527. Boston/Cambridge ranked lowest in jobs (fourth with 115,942, according to JLL), though MassBio recorded 79,972 statewide jobs in 2019).

San Francisco's DivcoWest signed Bristol-Myers Squibb (BMS) to a 360,000-square-foot lease at 250 Water Street within its Cambridge Crossing campus, set for completion in 2022. Sanofi sold its 310,000-square-foot plant built by its Genzyme subsidiary in Boston's Allston section to Resilience, a La Jolla, CA-based provider of biopharma manufacturing services, which has offered jobs to all 250 staffers and plans to add headcount. LA-based Breakthrough Properties inked a 263,500-square-foot lease with CRISPR Therapeutics at 105 West First Street ("The 105"), also opening in 2022.

Interest from top life sciences developers intensified in January: Alexandria Real Estate Equities shelled out $1.48 billion for office/R&D building 401 Park Drive, an office/lab building under construction (201 Brookline Avenue), and a future development site, all in Boston's Fenway section near Fenway Park, home of the Red Sox baseball team. Alexandria envisions a 1.8 million-square-foot "collaborative" life sciences campus with retail and common areas. Just north of Cambridge in Somerville, MA, BioMed Realty acquired an existing 162,000-square-foot office building and adjacent 7.5-acre site at Assembly Square, with plans for a 1.3 million-square-foot campus for research, technology, and life sciences users.

Top 10 Life Sciences Jobs Most in Demand over the Next Decade

Employment continues to trend higher through 2029, showing resilience against the pandemic

Source: PeopleImages/Getty Images

COVID-19 may have wreaked havoc on the U.S. economy last year, but it did not derail biotech employment. If anything, the pandemic is expected to stoke increasing numbers of jobs during this decade.

In assessing the impact of COVID-19 on the life sciences late last year, the world's largest commercial real estate services and investment firm CBRE Group cited U.S. Bureau of Labor Statistics figures in its U.S. Life Sciences Report 2020 to show that the nation's life sciences workforce dipped in June 2020 to 1.8 million jobs, just 1.3% below its March 2020 peak, and still 1% higher than a year earlier.

Moody's economy.com projected that employment in scientific R&D services will grow three times as fast as overall employment growth over the next five years—0.9% on average vs. 0.3% on average. By contrast, in the decade before COVID-19, scientific R&D employment grew 1.7% annually, compared with 1.4% annually for total nonfarm employment.

While Boston/Cambridge, MA and the San Francisco Bay Area retained their first and second positions on *GEN's* most recent A-List of Top 10 U.S. Biopharma Clusters, published March 10, neither lead the nation in total life sciences jobs (Los Angeles/Orange County, CA, ranks first, followed by New York/New Jersey). According to a March report from commercial real estate firm JLL, the nation's fastest-growing areas for life-sci employment are Seattle-Tacoma-Bellevue (3.1% higher growth in 2015–2020 vs. 2010–2015), followed by Atlanta-Sandy Springs-Alpharetta (3.0%).

"We all have personal losses to mourn, but we also have reason to be optimistic. The biotech industry is well-positioned for 2021, and I believe that it will land on its feet after all the upheaval. The same is true for hiring!" Meghan Williams-Pacini, Life Sciences Recruitment Specialist with the recruitment services provider GQR, wrote March 5 on the company's blog focused on COVID-19 and life-sci jobs.

"Job seekers will find that many things are different, but the fundamentals are the same," Williams-Pacini observed. "Hiring managers are still looking for a person who brings technical expertise and a strong cultural fit. More than ever, there is a large emphasis across the industry on effective communication, teamwork, collaboration, flexibility, and adaptability."

Below is a list of 10 research and clinical biotech occupations projected to add jobs through 2029, according to the U.S. Bureau of Labor Statistics' Occupational Outlook Handbook updated last September, ranked in order of the number of expected additional jobs to be created between 2019 and 2029, projected as of April 9. Each occupation also lists the number of jobs in 2019 as counted by BLS, the percentage increase between 2019 and 2029, the median pay per year in 2020, and a description of the position.

For seven of the 10 occupations highlighted in the Handbook, BLS projected smaller increases in jobs from 2019 to 2029 than it did between 2018 and 2028, the 10-year period BLS examined in the previous edition of its Handbook, the basis for *GEN's* 2019 A-List of top-10 biotech jobs most in demand. *GEN* published its first A-List of top-10 jobs in 2014, and published updated A-Lists in 2016 and in 2018. Two occupations showed increases in the 10-year job projections, while one showed the same projected employment change as in 2018–28.

10. Epidemiologists

Projected employment change, 2019-2029: 400 more jobs
Number of jobs, 2019: 8,000
Job outlook, 2019-29: 5% (Faster than average)
Median pay, 2020: $74,560 per year
About the position: Epidemiologists are public health professionals who investigate patterns and causes of disease and injury in humans. They seek to reduce the risk and occurrence of negative health outcomes through research, community education and health policy.

9. Genetic Counselors

Projected employment change, 2019-2029: 600 more jobs
Number of jobs, 2019: 2,600
Job outlook, 2019-29: 21% (Much faster than average)
Median pay, 2020: $85,700 per year
About the position: Genetic counselors assess individual or family risk for a variety of inherited conditions, such as genetic disorders and birth defects. They provide information and support to other healthcare providers, or to individuals and families concerned with the risk of inherited conditions.

8. Microbiologists

Projected employment change, 2019-2029: 600 more jobs
Number of jobs, 2019: 20,200
Job outlook, 2019-29: 3% (As fast as average)
Median pay, 2020: $84,400 per year
About the position: Microbiologists study microorganisms such as bacteria, viruses, algae, fungi, and some types of parasites. They try to understand how these organisms live, grow, and interact with their environments.

7. Zoologists and Wildlife Biologists

Projected employment change, 2019-2029: 800 more jobs
Number of jobs, 2019: 21,000
Job outlook, 2019-29: 4% (As fast as average)
Median pay, 2020: $66,350 per year
About the position: Zoologists and wildlife biologists study animals and other wildlife and how they interact with their ecosystems. They study the physical characteristics of animals, animal behaviors, and the impacts humans have on wildlife and natural habitats.

6. Bioengineers and Biomedical Engineers

Projected employment change, 2019–2029: 1,000 more jobs
Number of jobs, 2019: 21,200
Job outlook, 2019-29: 5% (Faster than average)
Median pay, 2020: $92,620 per year
About the position: Bioengineers and biomedical engineers combine engineering principles with sciences to design and create equipment, devices, computer systems, and software.

5. Biochemists and Biophysicists

Projected employment change, 2019–2029: 1,400 more jobs
Number of jobs, 2019: 34,600
Job outlook, 2019–29: 4% (As fast as average)
Median pay, 2020: $94,270 per year
About the position: Chemical technicians use laboratory instruments and techniques to help chemists and chemical engineers research, develop, produce, and test chemical products and processes.

4. Chemical Technicians

Projected employment change, 2019–2029: 1,900 more jobs
Number of jobs, 2019: 68,100
Job outlook, 2019–29: 3% (As fast as average)
Median pay, 2020: $49,820 per year
About the position: Chemical technicians use laboratory instruments and techniques to help chemists and chemical engineers research, develop, produce, and test chemical products and processes.

3. Medical Scientists

Projected employment change, 2019–29: 8,400 more jobs
Number of jobs, 2019: 138,300
Job outlook, 2019–29: 6% (Faster than average)
Median pay, 2020: $91,510 per year
About the position: Medical scientists conduct research aimed at improving overall human health. They often use clinical trials and other investigative methods to reach their findings.

2. Biological Technicians

Projected employment change, 2019–29: 4,300 more jobs
Number of jobs, 2019: 87,500
Job outlook, 2019–29: 5% (Faster than average)
Median pay, 2020: $46,340 per year
About the position: Biological technicians help biological and medical scientists conduct laboratory tests and experiments.

1. Clinical Laboratory Technologists (Medical Laboratory Scientists) and Technicians

Projected employment change, 2019–29: 24,700 more jobs
Number of jobs, 2019: 337,800
Job outlook, 2019–29: 7% (Faster than average)
Median pay, 2020: $54,180 per year
About the position: Clinical laboratory technologists (also known as medical laboratory scientists) and clinical laboratory technicians collect samples and perform tests to analyze body fluids, tissue, and other substances.