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The cell & gene therapy market matures

Wave of collaborations accelerate vaccine development

Dealmaking in 2020 faces new challenges

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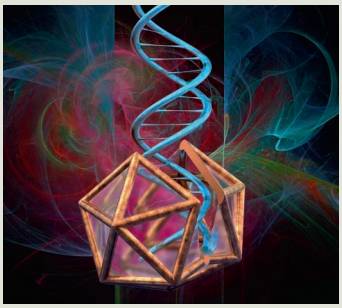

Cover image Gene therapy conceptual illustration; a double stranded DNA (deoxyribonucleic acid) molecule coming out of a viral capsid. Science Photo Library / Alamy Stock Photo.

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Profiles of organizations are aligned with relevant editorial features that cover different therapeutic and technological themes in each issue.

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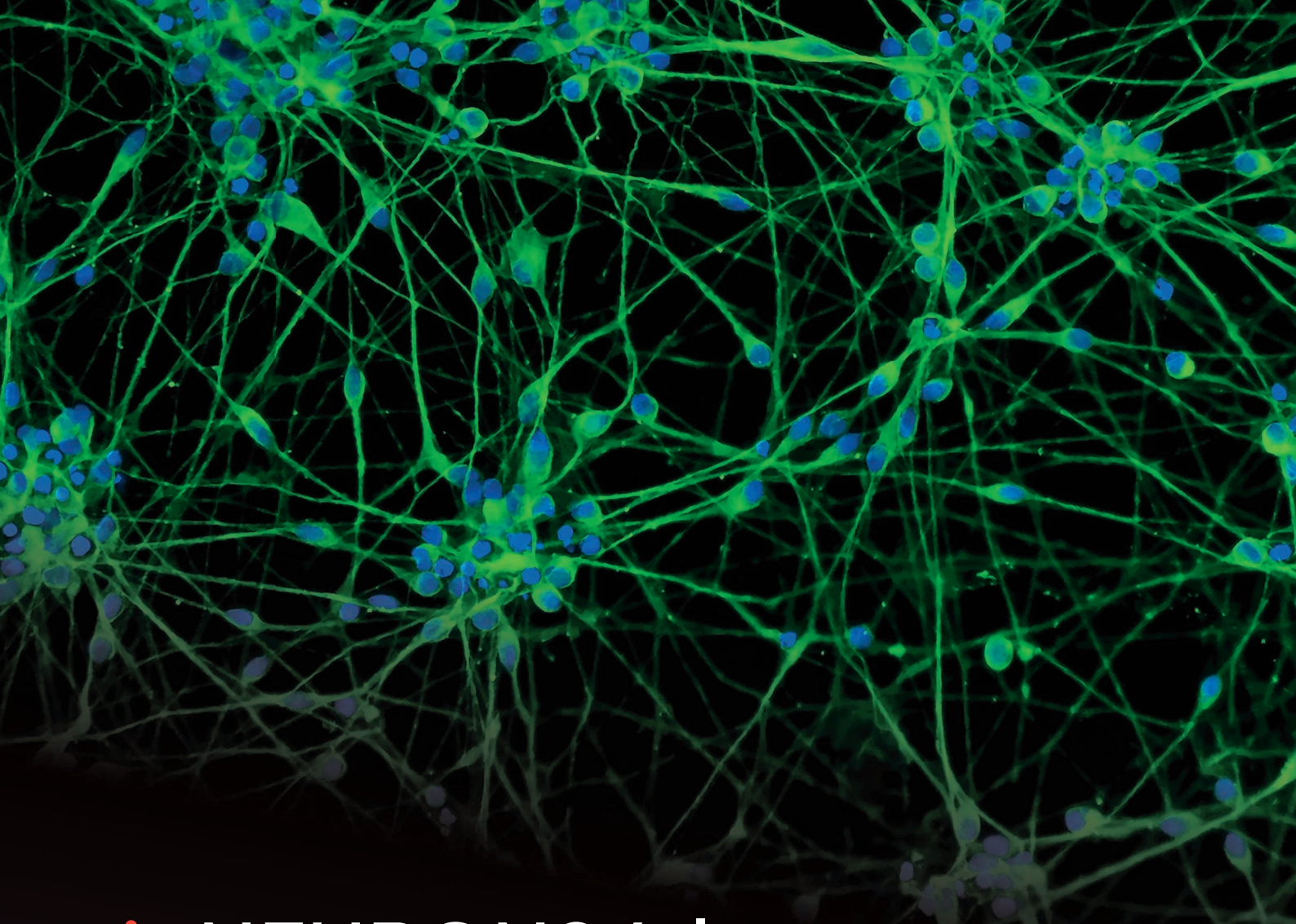

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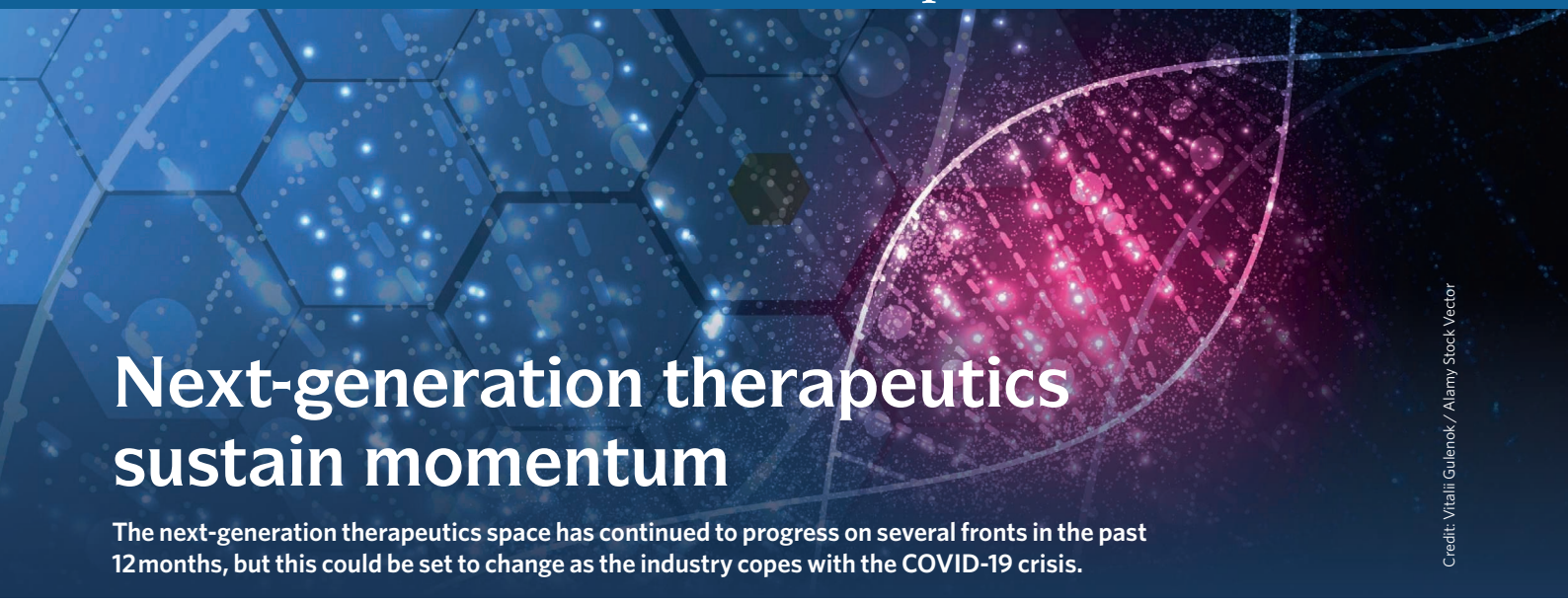

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Next-generation therapeutics sustain momentum

The next-generation therapeutics space has continued to progress on several fronts in the past 12 months, but this could be set to change as the industry copes with the COVID-19 crisis.

Paul Verdin

In April 2019, the combined 2024 sales forecast for the cell, gene and nucleic acid therapy market was $41 billion, according to EvaluatePharma sell-side consensus forecasts (*Biopharma Dealmakers* B15–17, June 2019). One year on, we analysed the area again, and here we highlight the latest trends in market forecasts, approvals, development pipeline focus, leading companies and dealmaking for next-generation therapeutics.

Fluctuating forecasts

Although clinical progress has boosted the number of next-generation therapeutic products on the market since 2019, our analysis of the same landscape puts the overall forecast value in 2024 at $38 billion—a 7% contraction of commercial expectations (Fig. 1).

Forecasts fluctuate of course, and volatility in forecast commercial performance is to be expected in such a pioneering area. Looking beyond the headline value, however, reveals that forecasts for DNA and RNA therapeutics (such as antisense oligonucleotides) and gene therapy have remained relatively stable—cell therapy is where the largest declines are apparent, as forecasts have eroded by almost $3 billion (or approximately 20%) since this time last year (Fig. 2). It is too soon to say whether this is the beginning of a cooling-off of commercial expectations for some cell therapy approaches. However, perhaps it could reflect growing recognition of the strong competition in some areas such as blood cancers, as well as the access and affordability challenges that affect cell therapies in general. It is also too soon to assess the impact of the COVID-19 pandemic, which could dramatically affect future forecasts.

Key approvals

The past 12 months have kept up the recent approval momentum in the field. Among the new products with the greatest expectations is AveXis/Novartis's Zolgensma (onasemnogene abeparvovec), which became the first US Food and Drug Administration (FDA)-approved gene therapy for spinal muscular atrophy (SMA) in May 2019. This approval also set up an interesting dynamic within the next-generation therapeutics space, with Zolgensma launching into a market already occupied by Biogen's Spinraza (nusinersen, an antisense oligonucleotide). Both therapies target the underlying cause of SMA, but Zolgensma is theoretically a 'one-and-done' treatment, while Spinraza requires repeated administration. Zolgensma has checked Spinraza's growth and is forecast to be the leader in an increasingly crowded SMA market by 2024, with sales of $2.04 billion compared with $1.57 billion for Spinraza.

Vyondys 53 (golodirsen), the second of Sarepta Therapeutics' growing portfolio of exon-skipping antisense oligonucleotides for Duchenne muscular dystrophy (DMD), was approved by the FDA in December 2019. And in Europe, there was a first approval for bluebird bio, with a European Medicines Agency (EMA) nod for Zynteglo (autologous CD34$^+$ cells encoding the

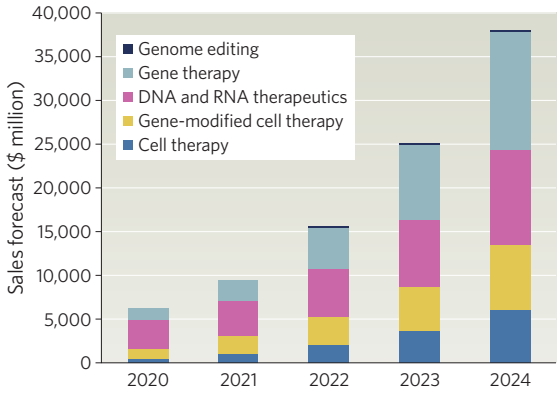

Fig. 1 | Sales growth forecasts of cell, gene and nucleic acid therapy products from 2020 to 2024. Source: EvaluatePharma, April 2020.

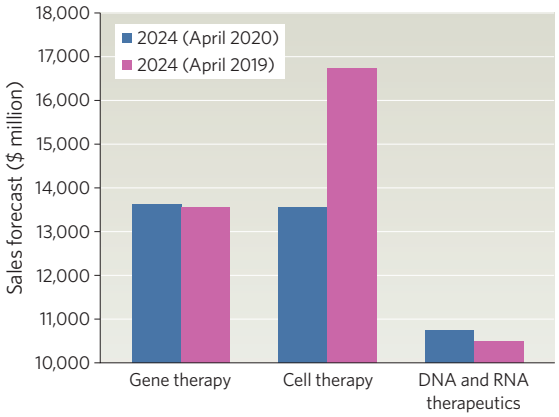

Fig. 2 | Changes in sales growth forecast trends of cell, gene and nucleic acid therapy products in 2024. Source: EvaluatePharma, April 2020.

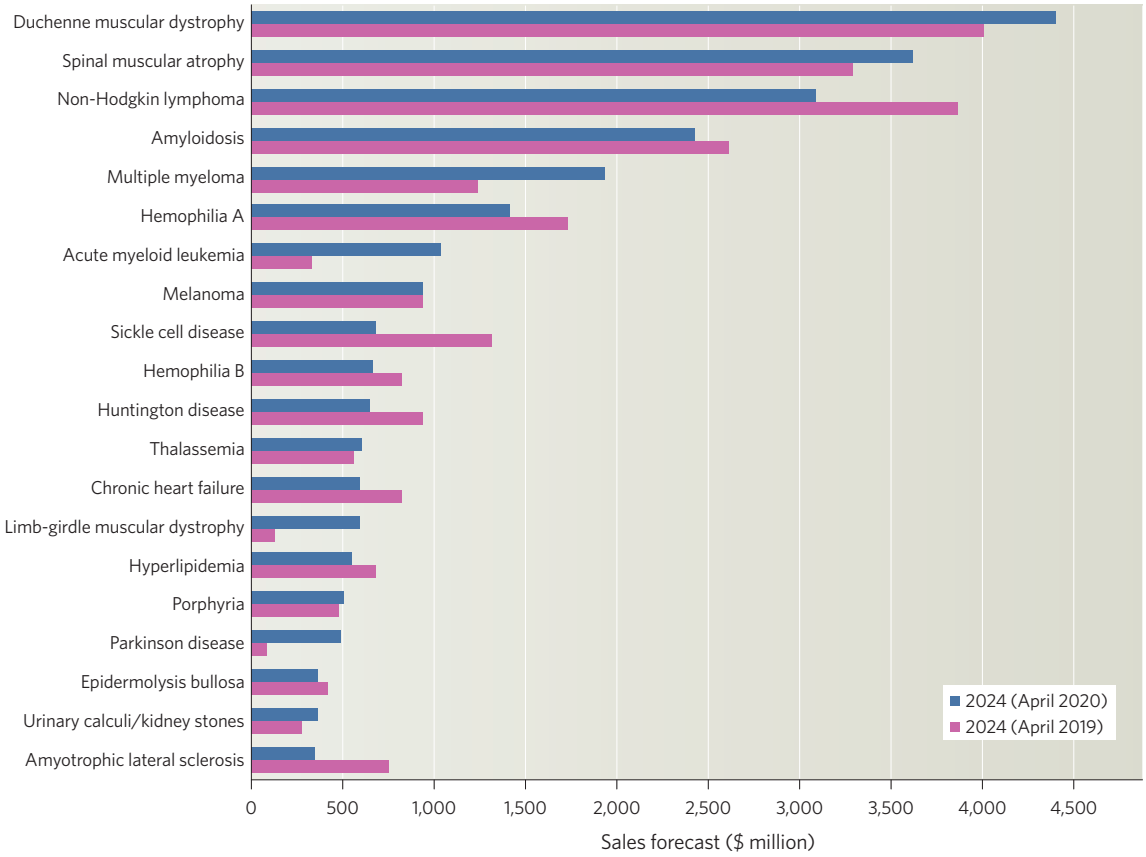

Fig. 3 | Top 20 indications in the field of cell, gene and nucleic acid therapies, based on 2024 sales forecasts. Source: EvaluatePharma, April 2020.

βA-T87Q-globin gene) for patients with β-thalassemia, as well as an EMA approval for Akcea/Ionis's Waylivra (volanesorsen), an antisense oligonucleotide therapy for familial chylomicronemia syndrome.

The scale and diversity of progress being made in the next-generation therapeutics space is a testament to the industry's ability and effort in developing novel science into commercial products. Across the industry, EvaluatePharma lists >5,300 active R&D programs in cell and nucleic acid medicine, an increase of 6% on the same analysis 12 months ago. Just over 2,000 of these next-generation therapeutic programs are in clinical development (an increase of 8% over 12 months), with more than 200 programs in phase 3 trials or at the regulatory filing stage.

Leading indications

Current clinical development pipelines in the field have a large focus on oncology, with 16 of the top 20 indications in cancer. The most studied non-oncology indications are rare ophthalmology conditions, Parkinson disease, osteoarthritis and peripheral vascular disease (Fig. 3). In preclinical research, the trend is different: 13 of the top 20 most studied indications are outside oncology.

Looking at where the value is anticipated to rise, at least in the near term, the picture is similar to 12 months ago. The top ranked indications by 2024 sales are those for which next-generation therapeutics are more clinically and commercially mature, with DMD, SMA and non-Hodgkin lymphoma topping the rankings.

Interestingly, 2024 forecasts for DMD are based on substantial sales growth from pipeline products: of the 10 next-generation therapeutics contributing to the 2024 sales forecast of $4.4 billion only two are currently marketed—Sarepta's Vyondys 53 and Exondys 51 (eteplirsen)—and 80% of this forecast figure is tied to R&D-stage programs. For SMA, the picture is the opposite: two of the three products contributing to 2024 sales are already marketed (Zolgensma and Spinraza), and >99% of the 2024 forecast of $3.6 billion is contributed by these marketed products.

The risk inherent in these forecasts is therefore very different, even without factoring in uncertainty around commercial performance once on the market. Across the top 20 indications by 2024 sales, only 6 are currently validated to the extent of regulatory approval and so clearly the space will continue to be highly dynamic.

Companies taking the lead

This dynamism is also reflected in the company rankings (Fig. 4). This time last year Sarepta led the pack in terms of 2024 forecast sales, and few major biopharma players featured in the top 20 by forecast revenues. Again, only 5 of the top 20 companies are large biopharma: Novartis, Bristol-Myers Squibb (following the acquisition of Celgene), Biogen, Gilead and Roche. In this year's analysis, however, Novartis leapfrogs Sarepta—albeit marginally—to become the top-ranked company in the field, with sales forecasts of $4.25 billion versus Sarepta's $4.14 billion in 2024.

Indeed, something of a niche is opening up in an otherwise highly fragmented landscape, with Novartis and Sarepta cementing

Methodology box

This analysis used data extracted from EvaluatePharma (data extracted in April 2020). Company and total product sales forecasts are Evaluate Consensus Forecasts, and represent an unweighted average of up to six forecasts from equity analyst research. Sales by indication are adapted from total product sales using a proprietary methodology. Historical sales, R&D pipelines and product classifications are based on company-disclosed information. All analysis, modelling, mapping and aggregation of data uses proprietary Evaluate methodologies.

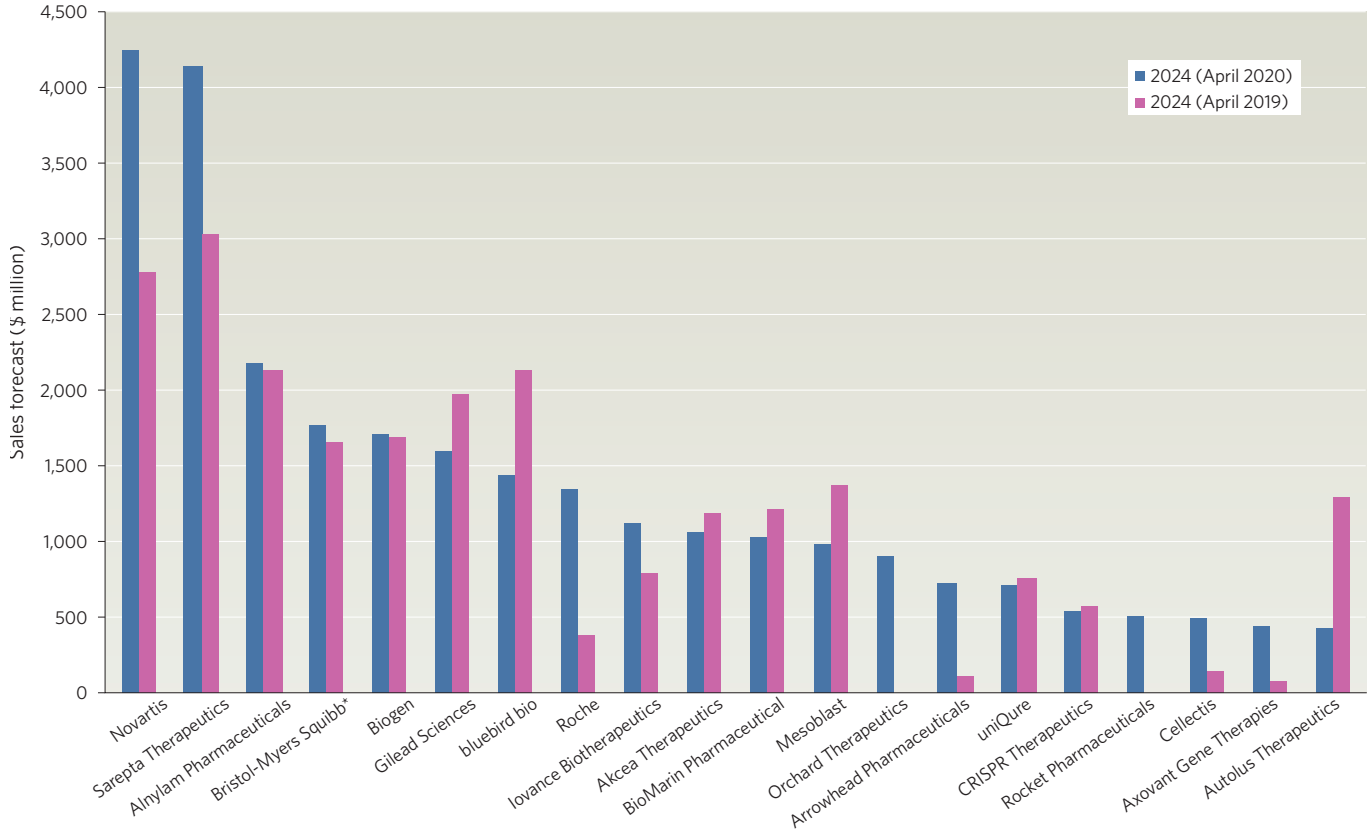

Fig. 4 | Top 20 companies in the field of cell, gene and nucleic acid therapies, based on 2024 sales forecasts.
*Celgene forecasts in Apr 2019. Source: EvaluatePharma, April 2020.

their leading positions and each expected to generate sales approximately double those of the next highest selling company in 2024 (Alnylam, in third place with $2.2 billion sales in 2024).

The Novartis portfolio delivering these sales is highly diversified, and includes the gene therapy Zolgensma for SMA (sales over $2 billion in 2024), the chimeric antigen receptor (CAR)-T cell therapy Kymriah (tisagenlecleucel) for blood cancers (sales over $1 billion in 2024) and the filed lipid-lowering RNAi candidate inclisiran (sales over $1 billion in 2024), which was obtained through acquisition of The Medicines Company in November 2019. For Sarepta, the near-term focus is on DMD, with far and away the biggest catalyst to 2024 being the micro-dystrophin gene therapy SRP-9001. Despite only being in phase 2 development, SRP-9001 is forecast to be the biggest-selling product in the cell and gene therapy space in 2024, with sales of more than $2.5 billion.

The remainder of the top 20 company ranking is comprised of numerous smaller and focused players, with several of their peers serving as take-out targets for major biopharma in the recent past—for example, AveXis, Spark and The Medicines Company.

Dealmaking trends

Major pharmaceutical companies have predominantly entered the space through acquisition. Novartis has been particularly active in building its leading position through acquisition—its $8.7 billion purchase of AveXis in 2018 was followed up in November 2019 with an even bigger pay-out of $9.7 billion for The Medicines Company.

Astellas is another major player that has been active at the deal table, picking up Xyphos Biosciences (CAR-T cell therapies) for $665 million in December 2019 and Audentes Therapeutics (gene therapy) for $3 billion in January 2020. Biogen continued its dealmaking in the space through the June 2019 acquisition of Nightstar Therapeutics for $800 million (gene therapy in ophthalmic disorders), and a February 2020 worldwide development and commercialization licensing deal with Sangamo Therapeutics for gene regulation therapies in Alzheimer disease, Parkinson disease and other neurological disorders (including $350 million upfront). In December 2019, Roche bought in to Sarepta's SRP-9001 through licensing of ex-US rights in a deal worth $750 million upfront and potentially up to $2.85 billion.

Outlook

On the face of it, progress in the next-generation therapeutics space continued unabated in the past 12 months—pipelines progressed, more innovative new products were approved by the regulators, deals were done and sales forecasts anticipating rapid growth in the space largely held up, barring some declines in cell therapy.

But it should be noted this activity predates the COVID-19 pandemic that has swept across the world. It seems unavoidable that the industry will feel a negative impact from this unparalleled crisis; for example, in delays to clinical trial progress and potential delays in regulatory approval for new products—and next-generation therapeutics will not be immune to this.

It is less clear how industry and societal thinking may evolve based on the impact of the pandemic; for example, in terms of allocation of R&D and healthcare spending, and prioritization of research into infectious diseases over rare genetic and oncology settings. According to EvaluatePharma data, <3% of currently active next-generation therapeutic R&D programs are focused on infectious diseases. Nevertheless, several of the most talked-about vaccines in development for COVID-19 are RNA-based approaches, and so the next-generation therapeutics space may have a key part to play in defining the exit strategy from the pandemic.

Paul Verdin is Head of Services at Evaluate Ltd.

Elicio Therapeutics Inc.
www.elicio.com

Orchestrating the immune system for precision immunity

Elicio's lymph node-targeting Amphiphile technology delivers potent T cell activation and boosts the effects of engineered cell therapies.

Immune cells are naturally gifted in recognizing antigens and fighting off infection and disease. But, just like talented people, they need nurturing and the right training to fulfil their true potential. For immune cells this means a spell in lymph nodes—the training camps of the immune system—where they receive specialized instruction in the art of immune surveillance and attack.

Today's immunotherapies do not make use of this powerful immunological form of education. The promise and effectiveness of immunotherapies are widely recognized: chimeric antigen receptor T (CAR-T) cell therapies directed against the CD19 tumor antigen have been particularly effective against hematological malignancies, and checkpoint inhibitors (CPIs) have emerged as a major focus for treating solid tumors.

Yet the full potential of these therapeutic approaches has not yet been unleashed. CAR-T cell therapies can struggle to achieve clinically beneficial T cell expansion and persistence, often lack the ability to effectively infiltrate the tumor microenvironment and over time lose their tumor-killing functions. At the same time, CPI therapies have demonstrated the ability of the immune response to kill solid tumors, but their efficacy has been limited because in these therapies few spontaneously arising T cells infiltrate tumors that have a low rate of neoantigen mutation. The key to overcoming these limitations, Elicio Therapeutics believes, is to make use of the specialized immunological training environment of the lymph nodes, to prime T cells to become more effective at their job.

Transporting immunomodulatory payloads

Elicio is tackling this challenge with next-generation immunotherapies based on its proprietary Amphiphile (AMP) technology, which can effectively ferry immunomodulatory payloads—from small molecules and peptides to DNA and proteins—to the lymph nodes, where immune cells learn how to recognize these immunomodulators and react appropriately to them. Elicio is applying the AMP platform to developing new cancer vaccines, creating more potent responses from CAR-T cells and delivering cytokines, immunomodulators and adjuvants to lymph nodes. The unique, broadly applicable lymph node-targeting AMP technology has the potential to address many unmet medical needs and bring enormous benefits to patients.

The AMP technology grew out of the multi-disciplinary lab of Darrell Irvine, a biological engineer at the Koch Institute for Integrative Cancer Research at the Massachusetts Institute of Technology. Irvine brought together materials scientists, immunologists and oncologists to work at the interface of materials science and immunology in an effort to solve the problem of how to target payloads to the lymph nodes.

Fig. 1 | A modular conjugation approach for delivery of immune therapeutics to the lymph node. The technology enables a lipophilic tail to bind to a linker domain, which is then able to attach to various types of immunomodulatory payload molecules.

Lymph nodes are one of the key secondary lymphoid tissues where immune cells congregate and where adaptive immune responses are initiated. It is here that the complex cellular interactions required for an effective immune response are finely orchestrated, and is why the lymphatic system is said to be the brain or command centre of the immune system. The learning environment of the lymph node endows immune cells with skills that are harder to learn elsewhere, such as how to achieve T cell expansion and persistence; how to effectively hone in on and penetrate solid tumors; and how to promote immune memory and antigen spreading.

Getting molecules of interest into lymph nodes, and making sure they stay there long enough to do useful work, faces some key hurdles. One of the most fundamental is that the smaller the molecule, the less likely it is to accumulate in the lymph nodes—an issue that affects small molecules, peptides, proteins and other biopolymers. The AMP strategy is to piggyback on a very large molecule, one that naturally accumulates in lymph nodes: albumin.

The core of the AMP technology is a lipophilic tail that mimics fatty acids that albumin naturally binds to, connected to a linker domain to which various types of immunomodulatory payload molecules can be attached (Fig. 1). When injected into tissue, cargo-loaded AMPs bind to locally present albumin, are transported through the lymphatic vessels and finally accumulate in lymph nodes. Here, the immunomodulatory payload ferried to the lymph nodes is taken up by antigen-presenting cells (APCs), which then interact with effector immune cells as part of their training to become potent antigen-targeting cells (Fig. 2).

Portfolio of candidates

Elicio has a range of candidates based on AMP technology in its proprietary pipeline: cancer vaccines that combine antigenic peptides and adjuvant with an AMP molecule; AMP-linked activators of CAR-T cells for hematological and solid tumors; AMP cytokines; and AMP adjuvants.

Elicio's most advanced cancer vaccine program is focused on patients with tumors carrying mutations in *KRAS*, which make up roughly 25% of all human solid tumors and are even more prevalent in specific cancers—up to 90% of pancreatic cancers, 50% of colorectal cancers and 30% of non-small-cell lung cancers. KRAS is widely recognized as promising in immunotherapy, and has been singled out by the National Cancer Institute as one of the only true public neoantigens, meaning that it is not only highly prevalent and clinically relevant, but also a target that the immune system is especially well suited to recognizing as a tumor-differentiating marker. And the biology of *KRAS* is compelling as mutations in this gene need to be maintained in all the tumor cells in most of the tumor types in which it is implicated. So if all tumor cells carrying *KRAS* mutations can be eradicated in a tumor, there is potential for a long, durable response.

Elicio's ELI-002 comprises AMPs carrying common *KRAS*-mutated peptides, along with a powerful immune-activating adjuvant, to elicit an immune response that engages both innate immunity (dendritic cells) and adaptive immunity (T cells) to increase tumor targeting. ELI-002 targets the seven position 12 and 13 *KRAS* mutations that are seen in more than 99% of *KRAS*-driven cancers,

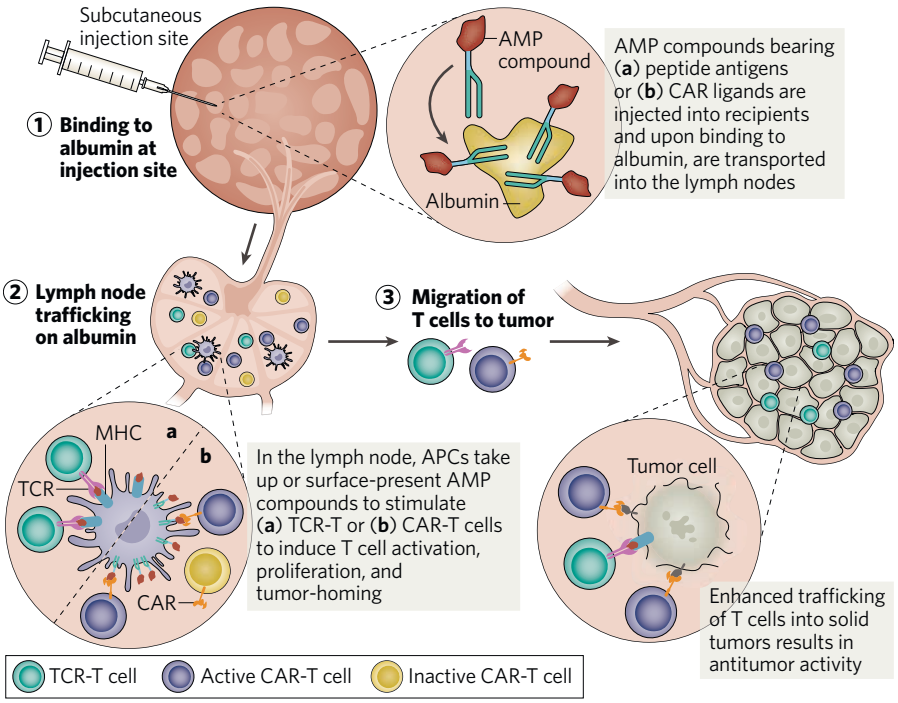

Fig. 2 | Targeting the lymph nodes with Elicio's amphiphile technology. Loaded with its immunomodulatory payload, the amphiphiles (AMPs) are injected into tissue where they bind to locally present albumin. From there they travel through the lymphatic vessels to gather in the lymph nodes. Antigen-presenting cells (APCs) in the lymph nodes then internalize or surface-present the AMP payloads to enable potent activating interactions with TCR-T or CAR-T cells, which empower them to seek out and destroy tumor cells. CAR, chimeric antigen receptor; TCR, T cell receptor; MHC, major histocompatibility complex.

and contains seven AMP peptides containing these mutations plus an AMP carrying a CpG Toll-like receptor 9 agonist.

Preclinical in vivo models have demonstrated that ELI-002 is precisely targeted to lymph nodes, where it creates a powerful T cell response that is more than 100 times greater than that achieved with conventional therapies. These lymph node-primed T cells, which become prolific producers of cytokines that are important for an effective antitumor response, are highly effective killers of KRAS-specific targets, and are able to specifically recognize all seven mutational variants of KRAS. Similar AMP vaccine approaches developed by Elicio and tested in other models have produced complete cures and resistance to otherwise lethal doses of tumor re-challenge.

In colorectal cancer care, patients with KRAS mutations are excluded from treatment with monoclonal antibodies against epidermal growth factor receptor, so that a therapeutic candidate for this subgroup holds potential to address a large group currently in need of an effective therapy.

Elicio is poised to begin a prospective, multicenter phase 1/2 clinical trial of ELI-002 in patients with locally advanced pancreatic ductal adenocarcinoma, colorectal cancer and other tumors after standard therapy. In the clinical trial of ELI-002, patients will be screened to identify those with tumors containing *KRAS* mutation and with minimal residual disease assessed by the presence of circulating tumor DNA—a group of patients that almost universally relapse. The trial is designed to allow crossover of patients assigned to the control arm to ELI-002 at the time of relapse, so that RECIST radiographic data on metastatic disease can be assessed. The trial is planned to begin in 2020.

Elicio has recently begun a collaboration with James Yang's laboratory at the National Cancer Institute, which has pioneered T cell therapies for solid tumors, to characterize T cell responses to ELI-002 in mice genetically engineered to carry human leukocyte antigen (HLA) genes important for the immune response. This study will not only inform how patient responses are monitored in the clinical study of ELI-002, but will also help use trial data to identify novel T cell receptors for future T cell therapies.

Elicio's other major application of AMPs is to unleash the full potential of CAR-T cell therapies. CAR-T cell therapies have demonstrated remarkable therapeutic results and have been shown to completely eliminate tumors in some forms of cancer, especially hematological malignancies, in some patients. Yet they have failed to show similar benefits in most other cancer settings, with solid tumors posing a particular challenge—largely due to the fact that current CAR-T cells lack the ability to properly expand their numbers, to efficiently infiltrate solid tumors and to effectively kill cancer cells. A major reason for these limitations is that CAR-T cells, as currently used, do not engage the lymph nodes at all. As a result, they are not activated at these key immune-orchestrating sites, and miss out on the education and training that lymph nodes provide to ensure that T cells become the best cancer-destroying cells they can be and remain functional and expanded over time.

Elicio is using its AMP technology platform to bring out the best in CAR-T cell therapies. The approach is to attach CAR-T activators to AMPs, which, once carried to lymph nodes by albumin, insert themselves into the surface of APCs through their fatty acid tails. These APCs then present the activator molecules to CAR-T cells in the lymph nodes, priming them to mount a potent response to tumor cells carrying the antigen they have been engineered to recognize (Fig. 2).

Elicio's proof-of-concept studies have shown how effective AMP CAR-T activators are. In a standard CAR-T cell approach, at best 20% of a patient's T cells are converted to recognize the tumor antigen that the CAR-T cells have been engineered to detect. When combined with AMP CAR-T activators, however, this jumps to as much as 70% or more in animal models. In addition, a number of current CAR-T therapies that have shown potent anticancer activity have been hampered in practice by toxicity caused by the high doses required for systemic delivery. The AMP technology can rescue these CAR-T therapies by targeting lower doses to the lymph nodes so they become highly effective tumor-destroying cells, while limiting exposure to other sites in the body.

Compared with CAR-T cell therapy alone, Elicio's AMP–CAR-T combination leads to a tenfold increase in the infiltration of solid tumors, a tenfold greater cytokine response, enhanced cytolytic function and the induction of 'antigen spreading', in which the native immune response is triggered to recognize tumor-specific antigens other than the one targeted by the CAR-T cell. In models in which CAR-T cell therapy by itself provides no detectable therapeutic effect, the AMP–CAR-T combination leads to durable cure in a large proportion of animals.

Beyond developing AMP cancer vaccines and CAR-T cell activator, Elicio is developing ELI-004, an AMP-adjuvant with applications in a variety of indications and therapies, including as the adjuvant component of ELI-002. Finally, Elicio has earlier-stage programs using AMP technology to deliver cytokines, immunomodulators and other adjuvants to the lymph nodes for stimulating a potent immune response.

Immunotherapies have proved their worth, but for many specific therapies their full effectiveness has remained untapped, or they have been beset by problems linked to toxicity. AMP technology addresses both issues. Elicio's strategy is to continue developing AMP applications to expand the range of diseases to which it can be applied, and to focus on building a proprietary pipeline around this core platform. At the same time, Elicio is keen to partner with companies developing complementary technology, specifically in the cell therapy space, to usher in a new era of immunotherapies.

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Novel regenerative treatments for CNS disorders and cerebral stroke

Biotech start-up company NovaGo is developing human antibodies that stimulate nerve repair and regeneration following a stroke. The company's lead candidate anti-Nogo-A antibody (NG004) is ready for phase 1 trials, and it is looking for partners to develop it through the clinic.

Stroke is the leading cause of adult disability in the developed world, affecting approximately 33 million patients worldwide and costing more than €40 billion per year in direct and indirect costs in the EU alone. Following a stroke, rapid re-establishment of blood flow can reduce tissue and neuron injury, but there is no pharmacotherapy available that can regenerate damaged regions of the brain; the mainstay of stroke treatment is rehabilitation therapy, which typically results in only modest improvements or recovery of function, leaving more than half of stroke patients severely and permanently disabled. As the global incidence of stroke is increasing at the same time as death from stroke is declining, stroke is now a disease of chronically disabled survivors, many of whom lose their independence and are forced to live in nursing homes.

NovaGo Therapeutics, a biotech start-up company that develops human antibodies that stimulate nerve repair and regeneration, is set to address this large unmet medical need. The company's co-founder and president, Martin E. Schwab, previously discovered that neurite growth inhibitors prevent repair and regeneration in the central nervous system (CNS). Although needed for proper CNS development and maintenance, they obstruct the regenerative process following stroke or injury, limiting recovery of function. Schwab identified Nogo-A as a key inhibitor of axonal growth. Since then he has founded NovaGo Therapeutics to pursue the development of regenerative therapies for CNS disorders. A strategic partnership with biopharmaceutical company Neurimmune enabled the discovery of specifically targeted human-derived antibodies that block Nogo-A.

By inhibiting Nogo-A, NovaGo's lead anti-Nogo-A antibody (NG004) induces neurite outgrowth—not only near the injured site but also in contralateral or other areas of the brain. The neuronal sprouting, together with rehabilitation exercise, enables significantly more recovery of function than rehab alone (Fig. 1). "Unlike a neuroprotectant, our recombinant human monoclonal antibody allows neurons to make new connections," explained Eduardo Vianna, CEO. "This promotes the central nervous system's regenerative healing process and neurological recovery and should allow stroke patients to recover much more function."

Preclinical studies in rodent and non-human primate models demonstrate that anti-Nogo-A therapy is highly effective in enhancing nerve fiber repair and the formation of new fiber connections.

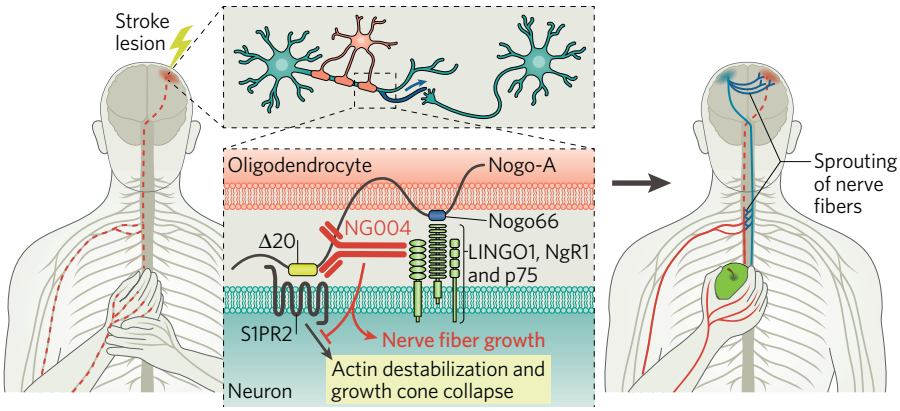

Fig. 1 | NovaGo's anti-Nogo-A therapy for stroke. The recombinant human monoclonal antibody NG004 induces neurite outgrowth by blocking the binding of Nogo-A to the Nogo-A receptor complex, preventing its activation (centre box). This allows neurons to make new connections, thereby promoting the neurological regenerative healing process, which in turn leads to a higher degree of functional recovery (right). Regeneration is observed near the injured site and in contralateral areas of the brain. This illustration is a prediction of how NG004 could work in humans based on data obtained from current animal models.

After a cerebral stroke, animals given the antibody for 2 weeks followed by 4 weeks of rehabilitation exercises recover 70–85% of function compared with only 40% for control animals receiving rehab alone. "Our anti-Nogo-A therapy boosts the sprouting of new nerve fibers, and the newly formed circuits are stabilized by intensive training," said Vianna. "Our results have overthrown the dogma in medicine that injuries of the brain and spinal cord will not heal and cannot be repaired."

Furthermore, the time window for administering the anti-Nogo-A therapy extends from days to weeks or even months after a stroke, enabling treatment of chronic strokes, months after the acute infarct.

Phase 1 trials are scheduled to start by the middle of 2021. A trial in patients with spinal cord injury is already ongoing and has shown that anti-Nogo-A therapies are safe and tolerable. However, high patient heterogeneity in stroke research presents a challenge, as recovery for each patient will depend on the type, size and location of the resulting lesion, their age, concurrent disorders and so on. Therefore, end points will include recovery of motor functions and quality of life assessment using stroke-specific scales. "Clinically, any improvement in nerve fiber regeneration and neural circuit repair is expected to have a strong impact on patients' outcomes and could dramatically enhance their quality of life," said Vianna.

Clinical studies partners

NovaGo's founding and management team has a proven track record in research and drug development, and maintains international networks across academia and industry, including close collaborations with the University of Zurich and the University Hospital in Zurich, Switzerland, where the company has its headquarters. NovaGo has started a series B investment round and is looking for suitable investors willing to participate as partners to support clinical studies of anti-Nogo-A through proof of concept to phase 2. "We are looking for investors who have an understanding of stroke and are willing to partner with us on this journey," said Vianna. "Our first-in-class regenerative therapy for stroke has a unique mechanism of action that leads to a large degree of functional recovery that could be life changing for sufferers of this debilitating and disabling condition."

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Biovian: a true one-stop-shop CDMO with gene therapy capacity and a Nordic ethos

Covering the whole production chain from the supply end to the value end, Nordic Biovian delivers a comprehensive and reliable manufacturing service, enabling the development of medical therapies.

Biovian is clearing bottlenecks in gene therapy production with its complete one-stop-shop service. Guided by its Nordic ethos, the contract development and manufacturing organization (CDMO) has built a reputation for delivering high-quality work on time and on budget to a global client base. Having done so, Biovian is continuing to expand its operation, adding scale and capabilities to support the development of breakthrough therapies.

'One-stop shop' is a term frequently used in the CDMO space, yet it is often poorly defined. Biovian views the concept along two axes, the supply chain and the value chain. To be a true one-stop shop, a CDMO needs to offer the full breadth of services along both the supply chain and the value chain.

Biovian meets that definition (Fig. 1). On the supply chain, Biovian's services span from master cell banking to qualified person release of the final labelled drug product.

Similarly, on the value chain Biovian's services run from preclinical supply up to commercial supply or manufacturing, enabling it to continue supporting clients as they take molecules through development and onto the market. At each stage, Biovian adheres to good manufacturing practice (GMP) and works out of fully inspected, fully certified facilities.

The breadth of Biovian's offering along both the supply and value chains differentiates it from some other CDMOs, which present themselves as one-stop shops but have gaps in their offerings that force clients to enlist other service providers for some work. Biovian is a true one-stop-shop CDMO.

Fig. 1 | Biovian offers clients a true one-stop-shop good manufacturing practice (GMP) contract development and manufacturing organization (CDMO) service, with modularity available from gene to finished vial.

How Nordic values guide Biovian

The clear definition of one-stop shop is in keeping with Biovian's straightforward, transparent approach to all communications and interactions with clients. As a Finnish CDMO, Biovian's approach is informed by the culture and world-leading education system of the Nordic region. Words such as quality, honesty and reliability that are inextricably linked to the Nordic region are embedded deep in Biovian's ethos.

That ethos can be boiled down to a simple statement: "We do what we say we will do." Those eight words capture the essence of Biovian's approach to clients, an approach that has enabled it to build a global customer base since it began operating in 2003. If Biovian says it will provide a deliverable by a particular date for a particular price, clients can be confident it will do everything in its power to do so.

Biovian's ability to live up to those expectations rests on its employees, who have the expertise and scientific skills needed for challenging projects. As importantly, having come through the Finnish education system, Biovian's staff share its focus on quality, honesty and reliability, values that are reinforced through the nature of interactions between the company and its employees.

By taking a straightforward, human-centric approach to internal and external relationships, Biovian has built a culture that prioritizes customer satisfaction and employee fulfillment equally. The result is a CDMO that is institutionally driven to deliver on its promises.

Investing to serve changing client needs

Biovian's strong relationships with employees and clients alike help it stay abreast of changes in the type of services biopharma companies need. Such insights helped Biovian to foresee the ongoing surge in demand for gene therapy manufacturing services and invest accordingly. Having done so, Biovian is easing two critical bottlenecks in gene therapy production today: viral vectors and plasmids.

In 2020, Biovian opened an expanded GMP viral vector manufacturing plant, more than doubling its capacity to make adeno-associated viruses, adenoviruses and other viral vectors vital to the delivery of gene therapies. Through the expansion, Biovian added a 200 l bioreactor, equipping it to continue to serve clients as they take gene therapies into late-phase clinical trials and onto the market.

Reflecting Biovian's definition of one-stop shop, that expansion along the supply chain was accompanied by an expansion along the value chain. Specifically, Biovian moved into the production of the plasmids that form the building blocks of viral vectors, making it a true one-stop shop for gene therapies.

Biovian is continuing to add to its capabilities. In 2021, the CDMO will open an aseptic filling line for recombinant proteins and plasmid DNA, adding to its existing biosafety level 1 and 2 viral vector fill-and-finish capabilities. The new fully automated filling line, which supports batches of up to 10,000 vials, features a restricted-access barrier system to ensure aseptic quality without sacrificing process flexibility.

The investments in viral vectors and fill-and-finish capacity are in line with the approach that has established Biovian as a premium CDMO. In a competitive market, Biovian has differentiated itself by pairing leading-edge production capabilities with its Nordic ethos, enabling it to deliver the materials clients need, when they need them, at the agreed quality.

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A new era of cell therapies for intractable diseases

Biotech company Cellatoz Therapeutics is developing innovative cell therapies by applying its proprietary cells, known as A-to-Z cells to multiple therapeutic areas. The company is now looking for partners to develop the therapies further.

Cellatoz Therapeutics is leveraging lessons learnt from the first wave of cell therapies to overcome barriers to the treatment of intractable diseases. Equipped with proprietary cells, Cellatoz is ushering in a new era for cell therapies defined by cell-specific markers and the regeneration of damaged cells or tissues. Now, having generated evidence that its approach has potential, Cellatoz is seeking a partner and funding to bring its cell therapies to patients.

Early attempts to use stem cells to treat disease failed to live up to expectations, with the harvesting and activation of primary cells and mesenchymal stem cells (MSCs) yielding therapies with marginal efficacy. The setbacks pointed to a new way forward for the field, leading Cellatoz to set out in 2017 to create reliable, novel, stem cell therapies.

Cellatoz's approach is based on proprietary cells, known as A-to-Z cells, with applications in multiple therapeutic areas. Rather than simply harvesting and activating primary cells and MSCs, Cellatoz is working with different starting materials and differentiating them to create therapies capable of treating intractable diseases.

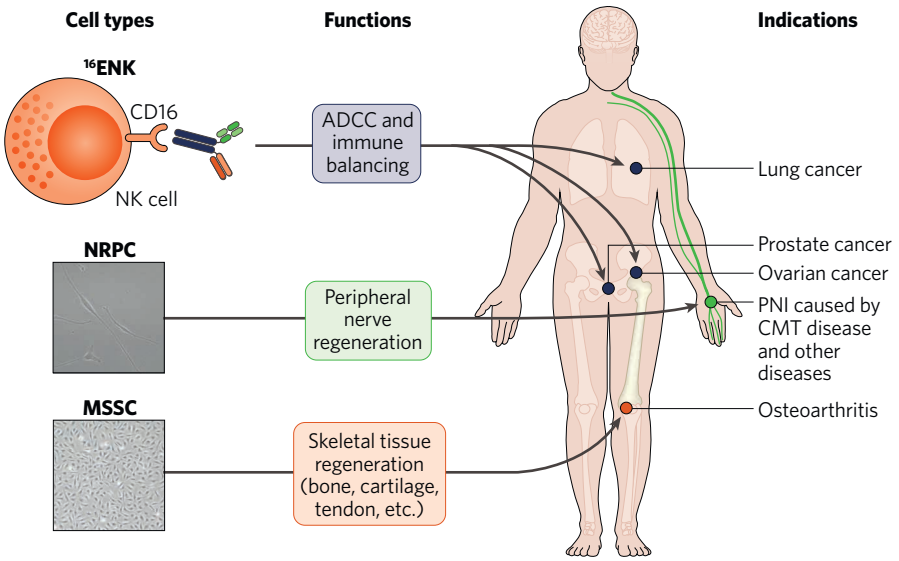

Fig. 1 | Applications of the proprietary A-to-Z cells at Cellatoz. The illustration shows the individual functions of each of the cell types and the diseases that they directly target. ^{16}ENK, CD16-highly expressing NK cell; ADCC, antibody-dependent cellular cytotoxicity; CMT, Charcot–Marie–Tooth; MSSC, musculoskeletal stem cell; NRPC, neuronal regeneration-promoting cell; PNI, peripheral nerve injury.

How A-to-Z cells treat disease

Cellatoz has discussed three applications of its A-to-Z cells to date (Fig. 1). In one program, Cellatoz is using pluripotent stem cells to create musculoskeletal stem cells (MSSCs) capable of differentiating into bone, tendon, muscle and cartilage. As the cells themselves, as well as the methodology and media used to make them, are proprietary, Cellatoz is in the process of establishing a thicket of patents. The protection is more comprehensive than is usual as ordinarily companies use non-proprietary cells.

There is evidence that Cellatoz's proprietary approach to cell therapy could translate into better outcomes. Nonclinical studies showed that a MSSC therapy, CLZ-1001, proliferates and differentiates at the injection site to regenerate bone tissue, thereby enabling recovery from severe injuries. Buoyed by the data, Cellatoz plans to develop CLZ-1001 as a treatment for osteoarthritis of the knee, either as a new drug or in combination with a medical device.

Cellatoz is advancing MSSCs in parallel to work on allogeneic neuronal regeneration-promoting cells (NRPCs). These Schwann-like cells are differentiated from tonsil-derived MSCs. By differentiating the cells, Cellatoz has improved on the efficacy of MSCs that are merely harvested and isolated. NRPCs secrete neurotropic factors to induce axon sprouting and remyelination of damaged nerves.

In light of those characteristics, Cellatoz is applying NRPCs, in the form of CLZ-2002, to the treatment of Charcot–Marie–Tooth (CMT) type 1A disease and other health conditions caused by damage to the peripheral nervous system. CLZ-2002 remyelinated sciatic nerves in an animal model of CMT, driving Cellatoz to start testing the cell therapy in another animal model[1].

Cellatoz is also developing autologous CD16-highly expressing natural killer cells (^{16}ENKs). Using a proprietary high-yield method, Cellatoz manufactures homogenized NK cells that express CD16 on their surface. Cellatoz thinks the presence of CD16 will lead to antibody-dependent cellular cytotoxicity, suggesting that ^{16}ENKs will work synergistically with immuno-oncology drugs.

Work is underway to validate that hypothesis by testing Cellatoz's lead ^{16}ENK, CLZ-3001, in ovarian cancer and other tumor types. As an autologous cell therapy, CLZ-3001 is suitable for repeat dosing, enabling Cellatoz the potential to treat cancer by rebalancing the immune system, rather than by just activating certain cells.

Taking the pipeline forward

Having raised a $10 million series A financing round in 2019, Cellatoz has advanced its lead programs into nonclinical studies with a view to filing investigational new drugs (INDs) in the first half of 2021. The work is taking place at a state-of-the-art research laboratory and good manufacturing practice (GMP) production plant that Cellatoz constructed to house its 35-person team.

The progress of the programs has led Cellatoz to seek support for the next steps. With the MSSC CLZ-1001 targeting osteoarthritis, a major indication, Cellatoz is seeking a partner to support clinical development of that drug candidate.

Cellatoz is taking a different approach to CLZ-2002 and CLZ-3001. As CLZ-2002 targets a rare disease, CMT, Cellatoz is talking to patient advocacy groups and plans to take that cell therapy forward itself using the proceeds of a series B round that it is in the process of raising. Cellatoz also plans to test CLZ-3001 in patients in Korea, its home market, and Japan itself before expanding globally.

Through the clinical trials, Cellatoz stands to validate the hypothesis that its A-to-Z cells could perform better than the first generation of cell therapies based on primary cells and undifferentiated MSCs. In doing so, Cellatoz will lead to the era of cell therapy 2.0, unlocking the therapeutic potential of human cells to tackle major unmet medical needs.

1. Park, S. et al. *Int. J. Mol. Sci.* **19**, E2393 (2018).

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A personalized approach to halting kidney disease

inRegen's personalized progenitor cell therapy injects autologous kidney cells (REACT) into patients' damaged kidneys, where cells migrate and restore kidney function. The cell-based treatment is showing signs of promise in ongoing phase 2 trials.

inRegen has developed a treatment for chronic kidney disease (CKD), now in phase 2 trials, that leverages a patient's own kidney cells to repair damage and improve kidney function. The approach is an auto-transplant of progenitor cells obtained via kidney biopsy and then reintroduced back into the kidney where they migrate to damaged kidney tissue, averting disease progression. According to inRegen CEO Tim Bertram, "Our personalized, autologous cell therapy doesn't require immunosuppression, is given as a simple injection, yet has unique potential to restore renal function lost to progressive CKD, transforming treatment and outcomes by delaying or preventing end-stage kidney disease."

Kidney disease affects ~850 million people worldwide. In the USA alone, 37 million people, half of them diabetic, suffer from CKD and are at risk of progressing to kidney failure. Arnold Silva, Director of Clinical Research, Boise Kidney and Hypertension Institute, and an investigator in inRegen's clinical trials, notes, "The full impact of CKD has been underappreciated, with little in the way of new treatments in the last two decades. Current therapies typically address the effects of reduced renal function, such as anemia, acid/base imbalance and hypertension, or underlying systemic disease, like diabetes and autoimmune disorders. inRegen's cell-based therapy treats the kidney itself, and may finally offer a means to stop or even reverse CKD progression."

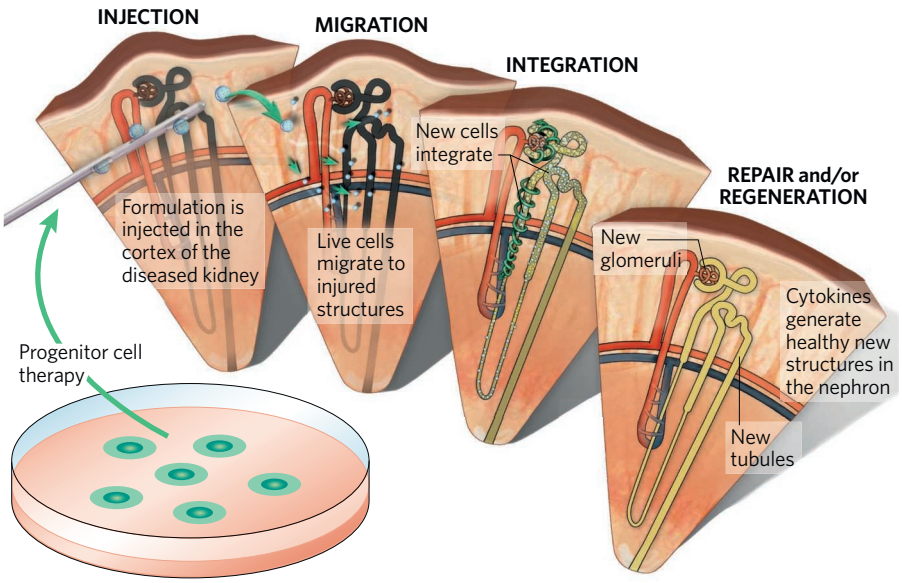

Fig. 1 | Renal progenitor REACT patient-derived cell therapy. Autologous kidney progenitor cells are injected into the kidney, where they rapidly migrate to diseased areas and integrate into nephronic structures (glomeruli and tubules), re-establishing kidney repair potential and restoring function.

Identifying kidney regeneration cells

Although kidneys are normally capable of recovering from acute injury, there is no current scientific support for the existence of a kidney stem cell. Undeterred by the decade-old challenge, with venture backing, inRegen scientists pursued a functional approach, systematically testing multiple kidney cell types in hundreds of combinations to deconvolute the activity in healthy kidneys responsible for regeneration in vivo. Their efforts ultimately succeeded in identifying a combination of cells able to form kidney tubules and Bowman's capsule in vitro. The cell mix included kidney progenitors with distinct phenotypic markers, including SIX2, OSR1, PAX2 and RET1. In preclinical studies, this combination of cells was able to induce new nephron formation, reduce disease and stabilize or improve multiple kidney functions, demonstrating long-term improvement in three different rodent models of severe CKD and a 70% nephrectomized canine model[1].

In the REACT (Renal Autologus Cell Therapy) clinical trials, patients undergo a kidney biopsy, and cells are isolated from the tissue under good manufacturing practice (GMP) conditions. The selected autologous, healthy progenitor cells are reintroduced into the kidney via injection on an outpatient basis, without the need for immunosuppression. The infused progenitor cells migrate rapidly to diseased areas, replacing damaged cells in tubules and glomeruli and regenerating new nephron structures (Fig. 1). The cells also localize in the interstitium, reducing fibrosis and inflammation, while modulating epithelial transdifferentiation. inRegen scientists hypothesize that kidney progenitor cells are programmed to heal damage, but in CKD become trapped by scars and effete from chronic inflammation, preventing normal function. This view is supported by the observation that these progenitor cells produce high levels of anti-inflammatory cytokines. By isolating and re-infusing these expert repair cells, inRegen's therapy may replenish natural reserves, allowing them to re-establish and maintain a healthy baseline function in the kidney.

Promising clinical trials

A first-in-human study with inRegen's progenitor cell-based treatment, conducted at the Karolinska Institute (Sweden), demonstrated that it was well tolerated. The therapy was granted US Food and Drug Administration fast-track status, and phase 2 trials in patients with diabetes with moderate to severe CKD were approved. Interim results of the randomized, controlled phase 2 trial showed earlier disease progression to dialysis in the control (standard-of-care) group compared with the REACT treatment group. The studies are nearing completion, with phase 3 trials slated to begin within the year. In addition, a phase 1 trial in adult patients with CKD due to congenital anomalies of the kidney and urinary tract (CAKUT) is currently enrolling in the USA and will be expanding to Mexico, where lack of surgical correction of CAKUT in childhood leads to a higher incidence of CKD in adulthood.

Kidney progenitor cells are highly sensitive to handling and prone to apoptosis. inRegen has developed proprietary methods to enable isolation, growth, formulation, and shipping of its cell-based therapy and holds extensive intellectual property (200-plus patents and patent applications) for composition, therapeutic use and methods of manufacturing. For patients in the on-going clinical trials, GMP manufacturing of autologous cell treatments is being conducted in partnership with Twin City Bio. inRegen plans to scale up clinical and commercial efforts to address the global scope of the unmet need in CKD.

1. Kelley, R. et al. *Cell Transplant.* **22**, 1023–1039 (2013).

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Synplogen

Using one-step DNA assembly to create designer DNA

Japanese company Synplogen uses technology based on over a decade of academic research to design and manufacture long and complex sequences of synthetic DNA. The company is also engaged in novel drug discovery and R&D of gene and cell therapies.

As the synthetic biology market continues to grow, there is increasing demand for longer length, error-free DNA of over 5,000 bp in length, sometimes much longer. These sequences of bespoke DNA are crucial for unlocking the power of synthetic biology for use in a wide range of sectors such as medical, industrial biotech, materials engineering, and the chemical, agricultural and energy sectors. However, creating these designer strands accurately, efficiently and cost-effectively can be challenging. Factors such as the length, complexity or repetitiveness of the sequence, or unusually high concentrations of certain types of nucleotides, often make certain desirable DNA sequences difficult or impossible to synthesize with currently commercialized methods. Synplogen's mission is to develop and commercialize technologies for the design and synthesis of these complex and high-value stretches of DNA, which are traditionally challenging to manufacture.

The origins of the technology

In 2003, Kenji Tsuge and his colleagues at the Mitsubishi Kagaku Institute of Life Sciences created a technology for the one-step assembly of DNA fragments into a strand of DNA with a specific order and orientation. The proprietary technology, known as ordered gene assembly in *Bacillus subtilis* (OGAB), grew out of a project to create hybrid bacterial genomes, as well as novel genomic DNA not found in existing organisms (Fig. 1). OGAB became the basis for Kobe City-based startup Synplogen, founded in February 2017 by Tsuge and Akihiko Kondo, now both company directors. In May 2019, Synplogen licensed another key companion technology from Kobe University for the combinatorial use of the OGAB method (combi-OGAB), which was developed by Tsuge during his time there.

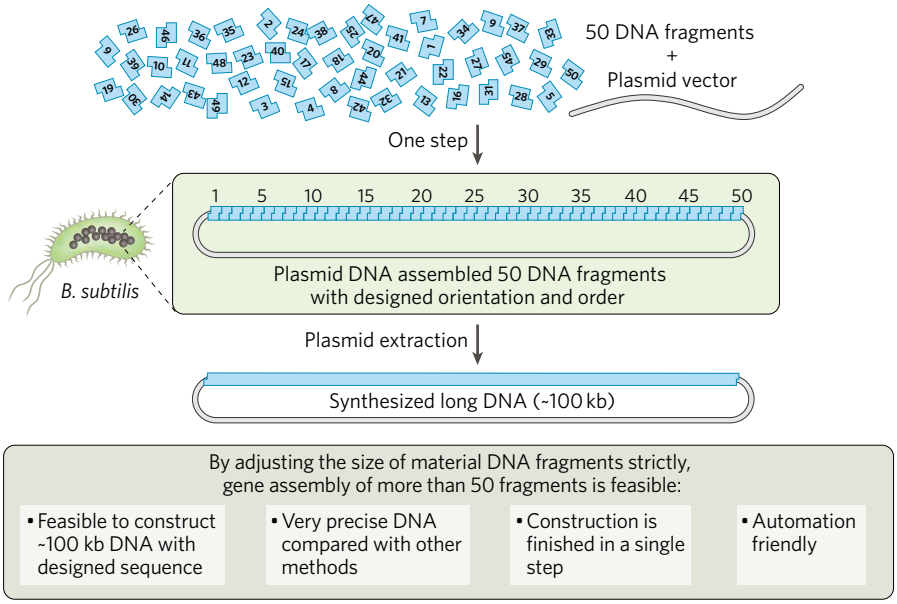

Fig. 1 | Synplogen's OGAB technology. Ordered gene assembly in *Bacillus subtilis* (OGAB) uses *B. subtilis* to assemble DNA fragments into a specific orientation and order to create long-chain DNA.

Creating longer length DNA using OGAB

Long chain DNA is constructed in vitro, using strands of genetic material of around 1,000 bp in length. These strands or 'blocks' of DNA then have to be linked together using cell-based processes. Many companies and researchers use *Escherichia coli* or budding yeasts for this process, but each of these techniques has its own challenges. On one hand, in the case of *E. coli*, as it can only take up circular DNA, an additional step is required to circularize the genetic material in vitro. However, the efficiency of in vitro circularization is low and becomes exponentially harder to achieve as the length of the linear DNA increases. On the other hand, yeast-based technologies can struggle with GC-rich DNA, especially at 70% or greater. To overcome these issues, Synplogen chose the well-characterized organism *B. subtilis*, known for its industrial use in the production of natto (fermented soya beans), to use as the basis for the OGAB technology.

Synplogen's OGAB-based platform can assemble linear DNA strands of up to 100 kb with very high precision. 50 or more DNA fragments, referred to as OGAB blocks, can be used with a success

rate of >95%, bringing a high level of fidelity to the assembly process. The naturally evolved plasmid transformation that occurs within *B. subtilis* can take up linear double-stranded DNA spontaneously and create a plasmid, meaning the OGAB process does not require a laborious DNA circularization step. Up to 50 fragments means that each OGAB block can be very short, and can be produced rapidly and efficiently through chemical synthesis. Additionally, *B. subtilis* has a faster doubling time and mutation rate than yeast, and Synplogen researchers have also so far seen no issues with mishybridization caused by GC-rich or repetitive sequences.

Following synthesis, the OGAB blocks are cloned as plasmids in *E. coli* to confirm the sequence. Highly equimolar concentrations of the fragments along with a plasmid vector allow *B. subtilis* to complete the plasmid assembly with great efficiency. Once the plasmids have been assembled in the desired orientation and order, they are extracted and the long strand of DNA is purified.

"Using this technique, which uses fewer assembly and sequencing steps than other approaches, we have been able to efficiently assemble many long, challenging genes, an example of which is a 100 kb human β-globin gene" said Tsuge. "We have also used OGAB in the successful construction of long-chain DNA with highly repetitive sequences, such as the genes for the enzyme non-ribosomal peptide synthetase (NRPS). NRPS is very exciting, but this enzyme has a modular structure, which has made it traditionally difficult to synthesize."

The company has created informatics solutions that have resolved restriction site issues, and automation has allowed for high-throughput manufacturing, greatly improving both the speed and accuracy of the process. All of this is improved iteratively, as data from experimental results are analysed through machine learning techniques. According to Kentaro Hayashi, Associate Director of Business Development, "We believe our synthesis platform can bring great value to our customers due to shorter delivery times and highly precise DNA."

Building combinatorial libraries for biopharmaceutical research

One of the important markets for long-strand DNA is biopharmaceutical and biomedical research. Between 1981 and 2010, around one-third of US Food and Drug Administration (FDA)-approved medicines were natural products or derived from natural products, and the number of genes and cell therapy products in clinical trials has dramatically increased over the past few years. Synplogen's combi-OGAB technology, as well as long-chain DNA, contributes to these fields, particularly drug discovery from natural products, gene and cell therapy development.

"Synplogen can create combinatorial DNA libraries by incorporating upwards of 10,000 different plasmids into each *B. subtilis* bacterium in a single step," said Shunsuke Saito, Associate Director of Business Development (Fig. 2).

Designing DNA de novo is a difficult process. Using a collection of OGAB building blocks creates a library of random repeat DNA around 100-fold more efficiently than making it from scratch. This is particularly effective for the rapid and effective optimization and activation of the gene clusters involved in the production of natural products in microbes.

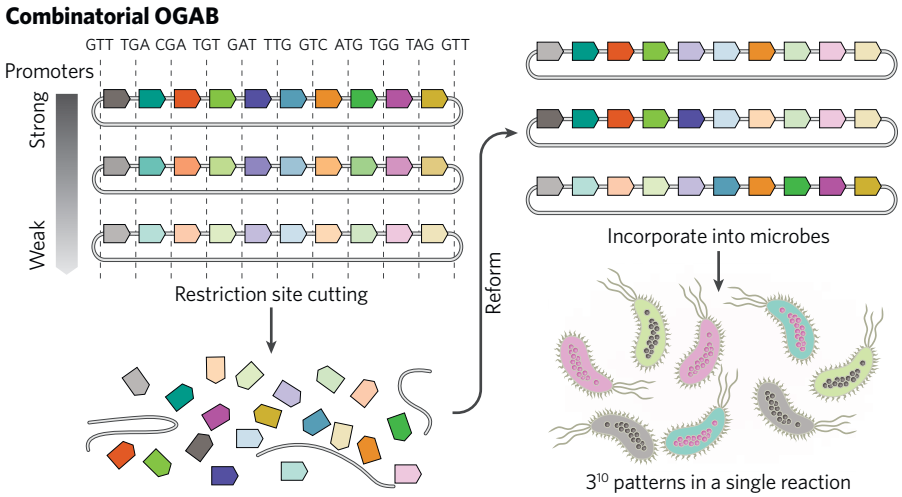

Fig. 2 | Creating combinatorial libraries using OGAB. Synplogen's combinatorial technology uses a collection of ordered gene assembly in *Bacillus subtilis* (OGAB) building blocks to create long stretches of random repeat DNA.

Beyond biotech and biomedical applications, the OGAB long-chain precision DNA and combinatorial DNA library technologies can also be used to design and create structural biomaterials and commodity chemicals; in agriculture for breed improvement and to lower the environmental impact of farming; and in biofuel production for greener energy.

> **"Synplogen can create combinatorial DNA libraries by incorporating upwards of 10,000 different plasmids into each *B. subtilis* bacterium in a single step"**
>
> Shunsuke Saito, Associate Director of Business Development, Synplogen

Taking the technology to partners

Synplogen has already established a number of partnerships in various fields. In October 2018, the new company announced a strategic collaboration with Spiber (https://www.spiber.jp/en), a Japanese company engaged in the design and production of alternative structural protein materials based on agricultural feedstocks. Synplogen received Japanese ¥100 million (about $1 million) in the deal, which it used for R&D and business development. Spiber's materials include spider silk- and cashmere-inspired fibers made using microorganisms. Structural proteins provide an almost endless opportunity to design and customize the material properties to a variety of end applications and could potentially replace other materials such as high-tech fabrics, steel and plastics. Working with Synplogen has given Spiber access to Synplogen's DNA manufacturing technology, accelerating Spiber's ability to design new proteins with exciting properties while also improving efficiency and reducing costs.

In July 2019, Synplogen also signed a strategic capital alliance with Tupac.Bio (www.tupac.bio), a biodesign and analysis software company based in Japan and the USA. The two companies are collaborating to develop software tools to improve and simplify gene synthesis and biodesign. These tools will be used to optimize and automate Synplogen's DNA synthesis process, allowing Synplogen to expand its capabilities. Synplogen has also gained access to Tupac.Bio's existing software tools.

The OGAB technology has a range of applications, and Synplogen is seeking further global partners from a range of industries across North America, Europe and Asia.

Making plans for the future

"We are working on an automation system that can rapidly generate assembly DNA and handle more DNA fragments and create longer stretches of DNA," said Hayashi.

By 2021, Synplogen plans to have expanded its Port Island, Kobe, location significantly, establishing an automated commercial production facility. This will increase floor space fivefold and production capacity by 15-fold.

"We plan to install new fermenters and establish research laboratories for viral vector development and cell and microbial engineering," said Saito.

The expansion has been funded by a third-party allotment of new shares to Japanese venture capital firm JAFCO for a total of Japanese ¥1 billion (about $10 million).

"Our new OGAB technology can generate DNA that was difficult to synthesize using conventional approaches. We will build a solid financial foundation from our DNA synthesis and DNA library businesses. Furthermore, we will maximize our business value throughout viral vector and engineered cell development for gene therapies. Currently we are seeking business partners who need our technology and want to develop projects together," said president and CEO Junichi Sugahara.

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Restoring the physiology of natural healing

Novadip is designing new treatment options for critical size defects, complex small size defects and surgically inaccessible tissue with its patented 3D tissue regeneration technology platform to transform the lives of patients with unmet medical needs.

Belgian company Novadip is focused on healing damaged bone and skin tissues by restoring their natural physiology. The company already has three new classes of products based on its proprietary 3M³ microRNA (miRNA) delivery platform, which utilizes adipose-derived stem cells and their 3D extracellular matrix (ECM).

The most advanced candidate is an autologous product designed to restore critical size bone defects. When tested in two young children with congenital pseudarthrosis of the tibia (CPT) it was shown to restore normal quality of life and avoid the need for amputation (Fig. 1). "Using Novadip's technology, we were able to develop a sufficient amount (20 cm^3) of autologous product to repair the affected bone and achieve direct continuity between the tibia and the fibula, enabling the child to walk without pain," said Denis Dufrane, CEO and founder of Novadip.

Founded in 2013 as a spin-out from the Catholic University of Louvain and St Luc University Hospital, Novadip is led by a reputed management team and supported by an international Scientific Advisory Board. The company has two clinical trials underway, a pipeline of seven products and a strong IP portfolio. To date, Novadip has successfully raised €50 million in equity and debt finance since 2015.

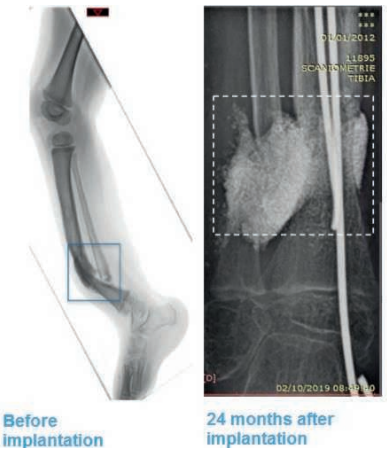

Fig. 1 | Novadip's candidate autologous product. The candidate product has restored normal quality of life in a child with congenital pseudoarthrosis of the tibia (CPT). Before treatment (left) the child was unable to walk. Complete bone fusion between the tibia and new bone formations was achieved at 24 months after implantation (right).

Three product classes

The 3M³ miRNA delivery platform is based on the virtuous cycle between adipose stem cells and ECM. "Our technology is designed to improve the release of specific miRNA from differentiated stem cells, which are integrated in a complex ECM in a 3D manner—it's really the interactions between the cells and the matrix that is the key," said Dufrane.

By varying the culture conditions and type of particle used, Novadip can also control the profile of miRNA release and create various 3D scaffold-free products, such as bone, skin, cartilage and skeletal muscle products (Fig. 2). The autologous cell products comprise cells, ECM, growth factors and miRNAs, and are designed to restore large tissue defects (>15 cm^3). The product is implanted directly in the affected tissue for critical size bone or skin reconstruction, in order to restore continuity with viable tissue.

An off-the-shelf allogeneic product line is being developed to treat defects in smaller but more complex environments such as multi-level spinal fusion, maxillofacial fractures, diabetic skin wounds and osteomyelitis. These products contain enriched ECM with the highly specific growth factors and miRNA preserved. They are in the form of a powder with biological activity and can be stored at room temperature. Novadip has demonstrated in vivo that its product candidates can promote tissue healing of bone and skin, with low immunogenicity for an allogeneic product.

Novadip is also working on a line of exosomal miRNA-based therapeutics for systemic tissue and other diseases, which is currently at an early stage of development. These products are being developed for local in situ or intravascular injection to address various potential indications, including systemic tissue diseases, such as osteoporosis and osteoarthritis, and certain solid tumors, such as osteosarcoma and melanoma. The company has isolated specific miRNAs from its autologous products and upregulated them with its 3M³ technology platform. "We have demonstrated in vitro that we can synthesize a specific pattern of miRNA into the exosome for specific cellular targets, so the next step will be in vivo proof-of-concept," said Dufrane.

Positioned for growth

To date, Novadip's product candidates have been used to treat 44 patients for bone reconstructions (up to 8 years of safety and full bone restoration in the context of tumor resection) and 6 for skin reconstructions (with a complete wound closure of a critical skin size defect >250 cm^2). Novadip owns a certified good manufacturing practice (GMP) facility in Belgium and is preparing for marketing scale-out.

NVD-003 is the most advanced program with a clinical proof-of-concept (POC) trial in CPT patients due to start in 2020 and first sales in this indication expected by 2025. NVD-003 is also being tested in adults with bone non-union in an ongoing phase 1/2a trial. Finally, a clinical trial is planned for NVD-002, which has demonstrated preclinical POC for critical size skin reconstruction.

Novadip is currently seeking further capital as part of a Series B to advance its clinical programs and R&D pipeline. This will include progressing clinical development of the autologous products for bone and skin indications, clinical POC of two off-the-shelf products and further preclinical development of cell-free exosomal miRNA-based products.

The market potential across all three product lines range could be worth in excess of $10 billion with future opportunities for partnering and licensing.

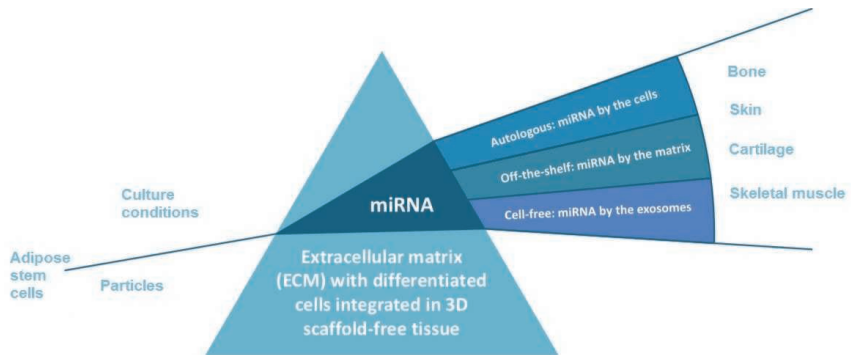

Fig. 2 | 3M³ miRNA delivery platform. By varying the culture conditions and particles, Novadip controls the profile of miRNA release through a 3D extracellular matrix. ECM, extracellular matrix; miRNA, micro RNA.

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Aruvant Sciences
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One-time gene therapy for sickle cell disease

Aruvant is developing ARU-1801, a one-time, potentially curative gene therapy for sickle cell disease and β-thalassemia. In an ongoing clinical phase 1/2 study, ARU-1801, administered with only reduced intensity conditioning, has provided stable reductions in disease burden and opioid dependence.

Sickle cell disease (SCD) is a progressively debilitating and life-threatening inherited red blood cell (RBC) disorder that causes a patient's oxygen-carrying RBCs to become abnormally inflexible and sickle-shaped upon deoxygenation. SCD causes anemia, frequent pain attacks and life-threatening acute complications such as vaso-occlusive crises. Furthermore, SCD shortens lives, with the median life expectancy for patients with SCD being just 42 years for males and 48 years for females.

Aruvant Sciences is a private clinical-stage gene therapy company focused on developing and commercializing transformative therapies for patients with severe hematological conditions. The company's near-term focus is on SCD, with a subsequent expansion into β-thalassemia. Aruvant's lead candidate, ARU-1801, consists of autologous cells that are genetically modified with a lentiviral vector that encodes a novel, highly potent anti-sickling γ-globin. ARU-1801 was designed to address the limitations of current curative treatment options, such as low donor availability and the need for more toxic, intensive chemotherapy conditioning regimens for stem cell transplants. The investigational therapy aims to restore normal RBC function through increasing levels of hemoglobin F (HbF) by increasing γ-globin protein levels (Fig. 1). γ-globin is a subunit of fetal hemoglobin, the primary form of hemoglobin in early life. Fetal hemoglobin exhibits a one and a half to two times higher oxygen affinity than normal adult hemoglobin, hemoglobin A (HbA). By enhancing the oxygen-carrying capacity of RBCs, the sickling process is prevented.

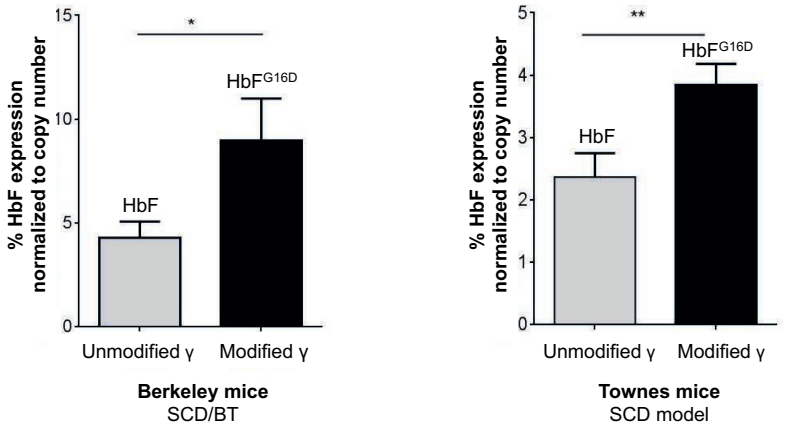

Fig. 1 | Aruvant's potentially curative gene therapy ARU-1801. ARU-1801 leverages a modified γ-globin, called γ(G16D), to produce a modified HbF called HbF^{G16D}. The γ(G16D) mutation results in higher HbF production per vector copy number relative to endogenous γ-globin. Significant improvement was seen in both the Berkeley (*$P < 0.05$) and Townes (**$P < 0.01$) mouse models.

A potent modified γ-globin

ARU-1801 uses a modified γ-globin to create a one-time, highly potent autologous treatment for SCD and β-thalassemia that requires only reduced intensity conditioning (RIC) for engraftment. ARU-1801 leverages a proprietary lentiviral vector to deliver a gene encoding a modified γ-globin, called γ(G16D), into a patient's own stem cells ex vivo. γ(G16D) was designed to have a higher affinity for α-globin, with the intention of outcompeting the mutated β-sickle chains and increasing fetal hemoglobin formation. Comparative studies of vector encoding γ(G16D) versus unmodified γ-globin show a higher proportion of fetal hemoglobin circulating in the bloodstream with γ(G16D) relative to unmodified, endogenous γ-globin.

Unlike other investigational gene therapies for SCD, the higher potency of γ(G16D) allows ARU-1801 to be transplanted using a lower, non-myeloablative dose of chemotherapy. Other gene therapies require the use of high-intensity myeloablative conditioning regimens to ensure sufficient engraftment to prevent sickling, typically resulting in lengthy hospital stays and a host of potentially serious short-term and long-term complications.

"We believe ARU-1801 has the potential to dramatically change the disease trajectory in patients with SCD and β-thalassemia," said William Chou, CEO of Aruvant. "The opportunity to receive a potentially curative gene therapy with a lower, less toxic dose of chemotherapy would provide a meaningful difference to individuals living with SCD."

Possible expedited development pathway for ARU-1801 in SCD

Preliminary clinical data to date from an ongoing phase 1/2 study in SCD patients have shown durable reductions in disease burden. Patients have shown stable levels of anti-sickling fetal hemoglobin levels at 21–29% of total hemoglobin for 15–21 months after treatment. Clinically, ARU-1801 has thus far resulted in reductions in vaso-occlusive crises and disease-related hospitalizations as well as discontinuation of daily opioid use. The US Food and Drug Administration (FDA) has granted orphan drug designation and rare pediatric disease designation to ARU-1801 for the treatment of SCD.

According to Chou, "side effects from conditioning chemotherapy such as infertility and long hospital stays often dissuade patients with blood disorders from choosing a curative therapy option. The ability to administer ARU-1801 through reduced intensity conditioning may open up the possibility of gene therapy to a broader group of patients."

Reaching beyond SCD

SCD is only one blood disorder that can benefit from Aruvant's modified fetal hemoglobin–based gene therapy. The company is already working on applying ARU-1801 to the treatment of β-thalassemia.

β-thalassemia is an inherited red blood cell disorder characterized by reduced or nonexistent production of functional β-globin, compromising the production of functional hemoglobin. Patients with the disorder suffer from anemia, which can cause weakness and fatigue. Aruvant is developing ARU-1801 as a therapy designed to boost levels of functional fetal hemoglobin in β-thalassemia patients and restore normal red blood cell function.

"At Aruvant, we are now focused on scaling up manufacturing and seeking alignment with the FDA and the European Medicines Agency for pivotal studies in both SCD and β-thalassemia," said Chou. "We believe we have a product that can change patients' lives; we come to work with a singular focus to successfully, rapidly, bring ARU-1801 to the many patients in need."

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Antapodia Nanotherapeutics
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ANTAPODIA NANOTHERAPEUTICS

Nanoparticle siRNA therapies halting metastasis

When primary tumors turn metastatic, prognoses become poor and survival time drastically shortens even with the best available therapies, including new immunotherapies. Antapodia Nanotherapeutics, Inc., is striving to meet the unmet needs of patients with advanced cancers with therapies that inhibit tumor growth and prevent metastases by targeting the common and key drivers of these malign processes.

One of the earliest events in the transition to a metastatic cancer cell is the development of finger-like projections called invadopodia that extend from the surface of the tumor cell. These invadopodia are able to dissolve the surrounding extracellular matrix (ECM) and act like feet that allow the cancer cell to 'walk' through the space created in the ECM. From here, invadopodia enable cancer cells to breach and enter the endothelium of blood vessels, travel to new locations in the body, then exit to establish new tumors. Antapodia has identified two proprietary master regulators of invadopodia—MIR-1, which is key to the initiation of invadopodia, and MIR-2, which maintains invadopodia—that the company is targeting with lipid nanoparticles carrying chemically modified small interfering RNA (siRNA).

Antapodia was founded by Patrick Yang—formerly Executive Vice President (EVP) and Global Head of Roche, EVP of Technical Operations at Genentech, and Vice President of Merck and JUNO Therapeutics—and Kelvin Tsai, a Harvard-trained Ph.D. and oncologist who co-discovered MIR-1 and MIR-2. Yang and Tsai are joined by a scientific advisory board with deep expertise in cancer metastasis, invadopodia and nanotherapy, including Robert Kerbel (University of Toronto), Kevin Struhl (Harvard Medical School), Yuval Shaked (Israel Institute of Technology), Avi Shroeder (Israel Institute of Technology) and Hon Leong (University of Toronto).

Antapodia has developed two candidate lipid nanoparticle siRNAs (LNP-siRNAs): AP-01, a first-in-class invadopodia-targeting therapy directed against MIR-1, a cancer-specific protein isoform, and AP-02, which similarly targets MIR-2, which mediates invadopodia signaling. In animal models of triple-negative breast cancer, non-small-cell lung cancer, liver cancer and pancreatic cancer, AP-01 both shrinks primary tumors and dramatically reduces metastasis (by up to more than 90%), and reduces mortality (by up to more than 80%). AP-01 has also been shown to synergize with the targeted agent sorafenib to achieve near complete remission—an effect also seen with high doses of AP-01 alone in liver cancer—without adverse toxicity.

Comparable results have also been found for AP-02, which targets MIR-2. AP-01 is approaching the Investigational New Drug Application-enabling stage, and Antapodia is keen to speak with potential investors and pharmaceutical companies who would like to hear more about joining Antapodia in its mission to bring these novel therapies into clinical trials within the next few years.

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Regenerative medicine cells to fight infectious diseases

MiCAN Technologies has developed Mylc cells, human myeloid lineage cells for use in the study of infectious diseases caused by viruses. The company is also developing a human red blood-like cell product, Mpv. It is hoped that, together, these products will accelerate vaccine and drug development globally.

MiCAN Technologies is applying regenerative medicine to the treatment of infectious diseases. After identifying a gap in the research toolkit, the Japanese company set out to develop human blood-like cells for use in the study of drugs and vaccines against infectious diseases. Having delivered on that objective, MiCAN is scaling up, expanding and globalizing to support the development of products that improve the lives of billions of people.

Kazuo Miyazaki, the founder and CEO of MiCAN, identified the need for a new approach to infectious diseases after seeing colleagues suffer from dengue fever and malaria. The treatments available to Miyazaki's colleagues were decades old and hindered by side effects and drug resistance, leading the now-MiCAN CEO to seek ways to use his years of regenerative medicine and pharmaceutical research experience to improve the treatment of such diseases.

That led Miyazaki to identify the availability of human blood cells as a barrier to progress. As these cells are targeted by infectious diseases, access to them would help researchers discover and test therapeutics and vaccines. However, neither donated blood nor hematopoietic stem cells provide human blood cells at the quantity, quality and cost needed, owing to issues that include low yields and differentiation processes that are difficult to control.

The lack of access to human cells is an impediment to infectious disease research. MiCAN, a startup out of INDEE Japan's Tokyo-based, hands-on accelerator ZENTECH DOJO, is set to clear that impediment using its new, better way to source human cells for use in infectious disease research.

MiCAN uses gene modification to immortalize monocytes and erythroblasts, before applying its differentiation method and stable production technique to create and grow human myeloid lineage cells and red blood-like cells. Using these core technologies, MiCAN is making human cells with the uniformity needed for R&D available at a cost that is low enough to enable widespread use.

Accelerating research into dengue and Zika

The human myeloid lineage cells, named Mylc, are the most advanced application of the approach, having come to market in 2019. MiCAN creates Mylc by immortalizing and differentiating peripheral blood mononuclear cells or induced pluripotent stem cells (Fig. 1).

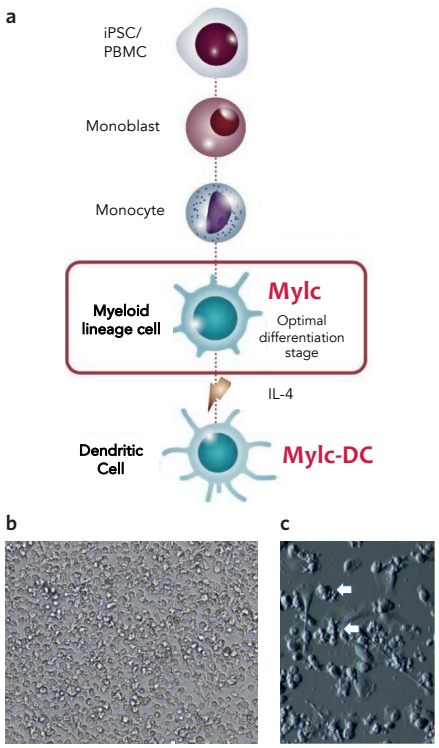

Fig. 1 | Application of MiCAN's technologies. **a**, Human myeloid lineage cells (Mylc) and dendritic cells (Mylc-DC) are grown by immortalizing and differentiating peripheral blood mononuclear cells (PBMCs) or induced pluripotent stem cells (iPSCs). **b**, Mylc cell. **c**, Mylc-DC cell.

Whatever the starting cell type, the process yields immature dendritic cells. These cells are the target of infection with dengue, Zika and other flaviviruses. Currently, researchers working on interventions against those major pathogens use monkey cells, namely, the Vero cell. However, these cells have a low sensitivity to infection and limited distribution.

Mylc cells are 1,000 times more sensitive than Vero cells, as MiCAN demonstrated in a study it presented at scientific meetings in 2019. The study showed that infection with dengue virus was impossible to detect in Vero cells below a multiplicity of infection (MOI) of around 6.4×10^{-5}. In contrast, Mylc cells were sensitive at an MOI as low as 5.1×10^{-8}.

The sensitivity of Mylc cells to infections caused by flaviviruses makes them potentially very useful tools to virologists in their current form. However, MiCAN is continuing to improve the product, for example, by transfecting the cells with GFP-tagged genes to monitor gene expression. In doing so, MiCAN may be able to identify Mylc cell lines that are even more useful to researchers.

Today, the need for such cell lines is greater than ever. With the COVID-19 pandemic creating a dire need for new therapies and vaccines, MiCAN is providing Mylc cells to academic scientists free of charge while running in-house research programs aimed at the SARS-CoV-2 virus.

Targeting protozoa and bacteria

The global availability of Mylc cells gives researchers studying infectious diseases caused by viruses a valuable new tool, but does nothing to help their peers who are focused on protozoal and bacterial pathogens. MiCAN is working to address those gaps in its portfolio.

A human red blood-like cell product, Mpv, is already in advanced development, with MiCAN now providing test and pilot products and preparing to start full-scale production. In Mpv, MiCAN will provide the infectious disease community with a source of the young red blood cells targeted by *Plasmodium vivax*, a protozoal parasite that causes malaria.

Researchers currently source cells from the blood of patients with malaria. The problem is that those cells are a seasonal material and suffer from low reproducibility. Mpv cells, in contrast, will be available all year round and have high reproducibility.

With MiCAN approaching the point at which it will provide tools to protozoal and viral researchers, the company is stepping up its efforts to develop a product for use in the study of bacterial diseases. By expanding its pipeline, MiCAN will use its regenerative medicine technologies and expertise to aid development of treatments and vaccines for the full spectrum of infectious diseases, delivering on the vision that led Miyazaki to found the company and helping researchers save lives.

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Partnering for a pandemic

History has shown that collaborative efforts can have a crucial role in combating viral outbreaks such as the current coronavirus pandemic.

Credit: S.Fenwick/ Springer Nature Limited

Raveena Bhambra

As coronavirus continues to spread, organizations around the world are working together to tackle the urgent needs for diagnostic, treatment and prevention strategies. In this article, we explore the wave of partnerships that have been established to accelerate the development of vaccines for the prevention of COVID-19.

Pandemic preparedness

In the past decade, the world has already faced two viral outbreaks that have caught regions off guard. In 2014, the Ebola virus surfaced in Western Africa. With an urgent need for infection control, but no approved therapies or vaccines and only a handful of vaccine candidates available, partnering was a must. A number of companies joined forces, including Johnson and Johnson (J&J), who partnered with Bavarian Nordic to develop a viral vector-based vaccine, and Merck & Co., who partnered with Newlink Genetics to rapidly develop and test its recombinant vaccine rVSV-ZEBOV (*BioPharma Dealmakers*, B15–17, June 2016). This candidate would eventually go all the way to be approved by the US Food and Drug Administration in 2019 as the first vaccine for Ebola. Now named Ervebo, it was already being applied from 2018 in another Ebola outbreak in the Democratic Republic of the Congo.

Shortly after the Ebola epidemic, Zika virus began to spread through South America in 2015. However, with relatively little known about the virus, researchers didn't have the head start they had with Ebola—similar to the current situation with COVID-19. Again, organizations and pharma companies came together to develop vaccines, and although the epidemic subsided by the end of 2016, several vaccines have progressed into clinical trials, putting potential responses to future outbreaks on stronger ground.

The responses to these two outbreaks highlighted the key need for coordination strategies and funding for efforts to combat future pandemics. Adding to established organizations such as the European Innovative Medicines Initiative and the US Office of Biomedical Advanced Research and Development Authority (BARDA), the Coalition for Epidemic Preparedness and Innovations (CEPI) was set up in 2017 specifically to coordinate the work of public, private, philanthropic and civil organizations for vaccine development to stop epidemics. And in the current crisis, CEPI has a key role in mobilizing funding and coordinating efforts for many organizations developing a COVID-19 vaccine.

Partnering at pace

Within days of the genome sequence of SARS-CoV-2, the coronavirus that causes COVID-19, being shared on 11 January 2020, biotech companies including Moderna, BioNTech, CureVac and Inovio Pharmaceuticals had started up vaccine development programs, with these front-runners taking advantage of the rapidity with which the underlying mRNA- or DNA-based platforms can be used to identify vaccine candidates. They were soon joined by others, ranging from universities and large pharma companies that are most active in the vaccine field in general, including Sanofi, GlaxoSmithKline (GSK), Pfizer and J&J. As of early May, almost 100 vaccines were being developed (*Nature* 580, 576–577; 2020), harnessing various platforms to design candidates, involving peptides, nucleic acids, virus-like particles, viral vectors, recombinant protein, live attenuated virus and inactivated viruses (*Nat. Rev. Drug Discov.* 19, 305–306; 2020).

Partnering has been crucial in tackling the challenges of highly novel vaccine discovery and development at such pace (Fig. 1). For example, Moderna—whose mRNA-based vaccine mRNA-1273 targeting the viral spike protein was the first to enter clinical trials in mid-March—was working on the candidate with the US National Institute of Allergy and Infectious Diseases (NIAID) just 2 days after the virus sequence was released, and shortly afterwards received funding from CEPI to support its development.

Given the likely need for vast amounts of any successful vaccines, adjuvants that enhance vaccine immunogenicity and make lower doses viable will be important. So, with only a small number of licensed adjuvants available, there has been a flurry of partnerships around them. Two vaccine big hitters, Sanofi and GSK, made headlines when they announced they would join forces. Sanofi will contribute its spike protein antigen, which is based on recombinant DNA technology, while GSK will contribute its adjuvant technology in the partnership. GSK and CEPI have established a collaboration to make GSK's adjuvant platform available to vaccine developers being funded by CEPI, and companies including Dynavax and Seqirus are also committed to making licensed adjuvants available to vaccine developers.

Finally, the need for large-scale manufacturing of successful vaccines has generated deals. For example, in March, Pfizer expanded an existing 2018 influenza vaccine partnership with BioNTech to co-develop and manufacture BioNTech's mRNA vaccines for COVID-19, which are notable in that the clinical trial program is testing four vaccine candidates, with different combinations of mRNA format and target antigen. And in April, AstraZeneca announced a partnership with the University of Oxford on the development, manufacture and distribution of their adenovirus-based vaccine targeting the spike protein. Moderna followed suit by partnering with Lonza to enable the manufacturing of up to 1 billion doses per year of its vaccine if it is successful—underlining just how big a challenge counteracting COVID-19 has become.

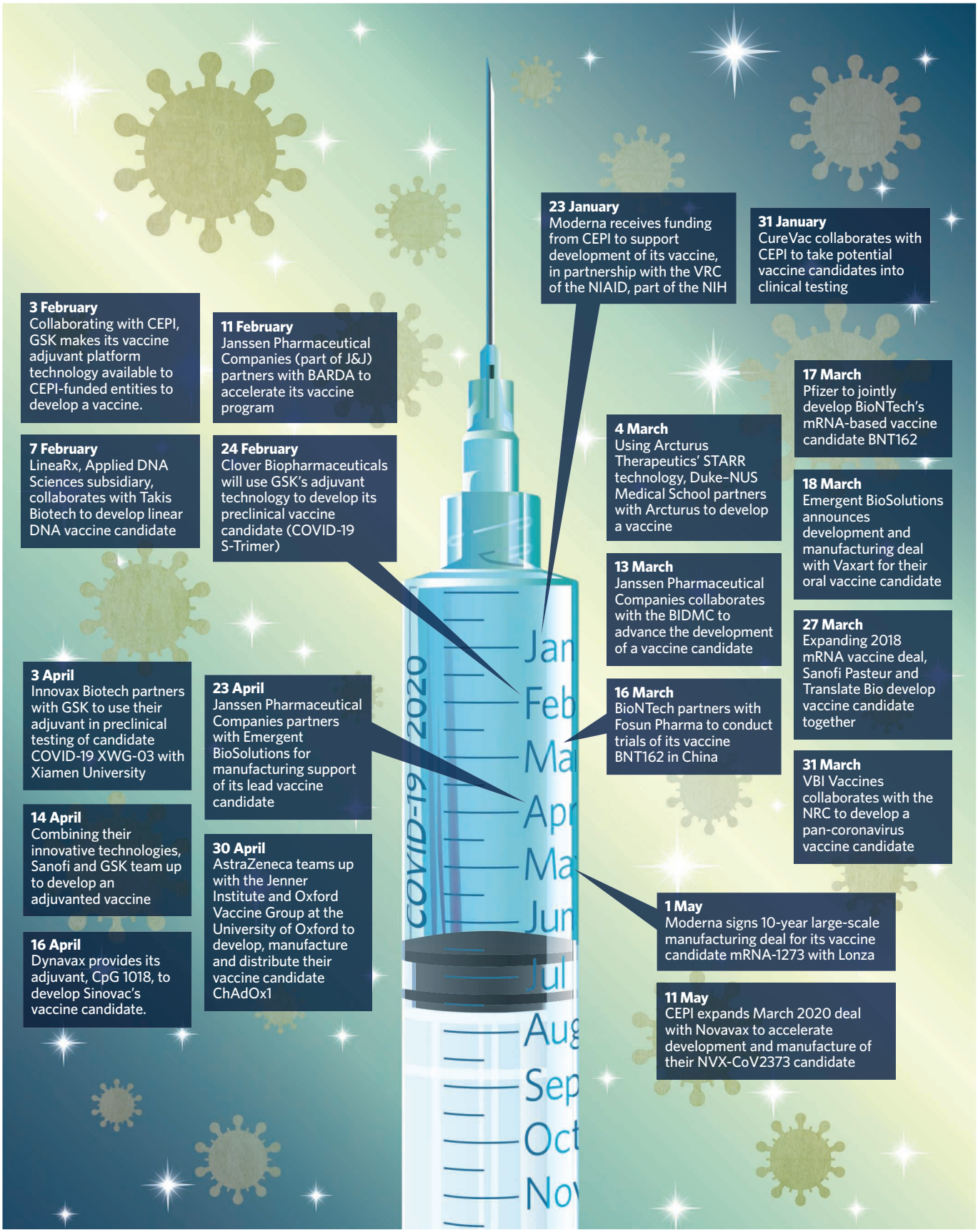


Fig. 1 | The world's most wanted vaccine. Selected biopharma partnering deals relating to the development, manufacture and distribution of a potential vaccine against COVID-19 in 2020. BARDA, Biomedical Advanced Research and Development Authority; BIDMC, Beth Israel Deaconess Medical Center; CEPI, Coalition for Epidemic Preparedness Innovations; J&J, Johnson & Johnson; NIAID, National Institute of Allergy and Infectious Diseases; NRC, National Research Council of Canada; VRC, Vaccine Research Center. Data taken up to 18th May 2020.

GSK Vaccines
www.gsk.com

Vaccines partnering to give your science and technology a global impact

GSK forms multidisciplinary teams to accelerate R&D and address major public health challenges

Advances in immunology, genetics and microelectronics are creating opportunities to improve human health. More work is needed to realize the potential of novel technologies. As a science-driven leader in vaccine research, development and production, GSK is well placed to collaborate with companies and universities to translate technologies into products that make a global impact.

GSK has a broad portfolio of vaccines to help protect people of all ages from infectious diseases. The portfolio is robust, with one quarter of sales coming from innovations introduced in the past 5 years. GSK is working to bring more advances to market, investing £718 million in core vaccines R&D in 2019.

A team of 2,500 GSK vaccine scientists at three R&D centres is focused on advancing 15 innovative assets in clinical development and moving new candidate vaccines into human testing. While GSK's scientists apply leading technologies, collaborating with external experts is an essential part of its strategy. GSK Vaccines has over 110 scientific collaborations and works with partners on all its pipeline prospects.

What GSK looks for in alliances

GSK is looking for scientific partnerships with large and small drug and vaccine developers, consortia, charities, academia—including graduate and postdoctoral research programs—and companies in industries beyond biopharma that can help adapt innovative solutions to vaccine challenges.

The relationships sought by GSK cover discovery to late-phase development projects that advance disease prevention and therapy, vaccine production and supply, and help transition from 'anchor' systems that define operations today to future digital technologies. Through such pacts, GSK is using, for example, reverse vaccinology and systems biology to accelerate vaccine discovery and development.

For all scientific partnerships, GSK applies the same open, collaborative and science-led ethos. Its R&D experts evaluate scientific and technological opportunities, focusing on scientific evidence, potential outcomes and impact, while trying to understand the needs of the possible partner.

GSK aims to establish creative collaborations that harness the strengths of each contributor to achieve shared goals. At GSK, scientists are entrusted with managing the relationship, ensuring close communication and ready access to resources. GSK is also building the next generation of vaccinologists by providing courses and opportunities for PhD students and postdoctoral researchers.

Areas of interest for potential partnerships with GSK Vaccines R&D

Immunology and vaccinology
- Are you developing new technologies to characterize and monitor host–pathogen interactions or immune responses?
- Are you researching epigenetic modification of innate immune cells (trained immunity)?

New vaccine targets and antigen design
- Are you researching novel associations between viral or bacterial agents and chronic diseases?
- Are you developing new tools to refine or accelerate future vaccine target identification?
- Are you developing nanoparticles or virus-like particles or other antigen delivery platforms?
- Are you researching monoclonal antibodies?

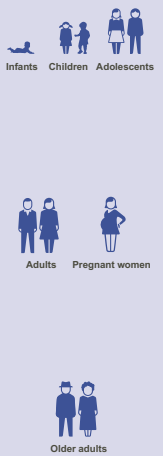
New technology platforms
- Are you investigating antigen stability?
- Are you working on microbiome functions?
- Are you working on technologies to induce more efficient and rapid immune responses?
- Are you researching structural vaccinology?

Vaccine delivery
- Are you developing mucosal, oral, sublingual, nasal or intradermal delivery methods or devices?

New production process technologies
- Are you developing new technologies to characterize biological products or improve their manufacture (biosensors, microfluidics)?

New technologies and tools to accelerate R&D
- Are you developing miniaturized clinical assays to make them faster and more robust or developing quality control and assurance assays?
- Are you developing novel clinical trial designs?
- Are you researching biomarkers and the application of systems biology to new readouts?
- Are you developing organoids or organ-on-chip systems?
- Are you developing assays on a chip?

Artificial intelligence and digital data analytics
- Are you investigating novel applications of systems biology, data modelling and analysis and artificial intelligence that could inform and accelerate the discovery and development of future vaccines?



How GSK is having a global impact

GSK has a broad vaccines portfolio with global reach and delivers around 2 million doses of vaccine every day to people living in more than 160 countries. It includes, for instance, vaccines against shingles (older adult), meningitis (pediatric and adult) and hepatitis (pediatric and adult). GSK also has a strong R&D pipeline of vaccine candidates including respiratory syncytial virus (RSV), therapeutic chronic obstructive pulmonary disease (COPD), therapeutic chronic hepatitis B, *Clostridium difficile* and *Shigella*.

The global impact of GSK's scientific partnership model is illustrated by its collaborations. As a recent example, multiple approaches will be necessary to stop the COVID-19 pandemic. GSK is making its vaccine adjuvant technology available to scientists and organizations working on promising COVID-19 vaccine candidates and technology platforms.

As part of the Innovative Medicines Initiative, GSK supports healthy aging by creating vaccines and vaccination strategies to overcome the age-related weakening of the immune system. GSK also joined the Respiratory Syncytial Virus Consortium in Europe (RESCEU) with teams from academia, patient groups, other pharma companies, regulatory agencies and others to share knowledge of RSV.

GSK is working with postdoctoral researchers and PhD students from Italian and UK universities to try to understand the role of the pathogenic bacteria most prevalent during acute exacerbations of COPD (AECOPD)—non-typeable *Haemophilus influenzae* and *Moraxella catarrhalis*—and elucidate the mechanism of action of a new vaccine candidate in development that aims to prevent AECOPD, by using next-generation in vitro models.

GSK established a partnership with Viome, a company with expertise in understanding the gut microflora and its role in chronic diseases, to facilitate vaccine development to prevent or treat such conditions.

Working with the Bill & Melinda Gates Foundation and the Wellcome Trust, GSK is developing a vaccine against *Shigella*, a genus of bacteria that causes the loss of 12.8 million disability-adjusted life years and 237,800 deaths a year. The rise of drug-resistant bacteria is reducing treatment options, intensifying the need for a vaccine.

A collaboration with the Université Libre de Bruxelles, Belgium, to characterize in-depth fermentation processes uses time-resolved state of the art omic methods coupled with data analytics and mathematical modelling. This characterization represents a step toward the digitalization of vaccine process development and aims to improve the overall vaccine quality and to hasten the development process.

Going forward, GSK continues to seek out such collaborations to gain access to technologies and knowledge that enable and accelerate the development of life-changing vaccines.

1. GHDx. http://ghdx.healthdata.org/gbd-results-tool (2017).

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Coating medical devices to fight infections

Amicoat's environmentally friendly antimicrobial coating technology has a broad spectrum of activity with a low risk of provoking antibiotic resistance. The peptide-based technology effectively eliminates biofilms and can be applied to a wide range of medical devices to reduce healthcare-associated infections.

Healthcare-associated infections (HAIs) pose a major risk to patients, especially in vulnerable and immunocompromised individuals, and this is accentuated in the context of the ongoing COVID-19 pandemic. In many cases HAIs are attributed to indwelling medical devices, such as wound dressings, catheters and intubation equipment.

Amicoat has developed a peptide-based antimicrobial coating (AMC) technology with activity against a broad range of pathogens. It can be applied to medical devices to reduce the incidence and complication of HAIs. "By integrating our AMC technology into their medical devices, original equipment manufacturers will be able to offer products with leading-edge properties to combat microbial infections, including those caused by antibiotic-resistant strains," said Georg Andreas Gundersen, CEO of Amicoat.

The patent-protected AMC technology offers several advantages compared with existing technologies such as silver- and antibiotic-based platforms. The active component, AMC-109, is highly effective at both eradicating and preventing biofilm and there is a low risk of bacteria developing resistance. The technology can be applied to a wide variety of surfaces and materials, e.g. polyurethane and silicone. It also has a benign environmental impact, degrading into simple amino acids.

Founded in 2014 in Tromsø, Norway, Amicoat is now entering into license agreements with original equipment manufacturers (OEMs) to use its AMC technology. Customers are supported throughout the product development process by the company's expert interdisciplinary team.

Rapid antimicrobial action

AMC-109 is a small synthetic antimicrobial peptide developed through extensive research on the antimicrobial properties of lactoferricin, a host-defense peptide fragment that can be found in humans and other mammals. Amicoat's scientists have harnessed certain characteristics of the peptide to improve it and make it suitable for application on different types of materials and devices.

The mechanism of action for AMC-109 is lysis of bacterial membranes—it attaches to the outer cell membrane of a bacterial cell and causes it to rupture and die rapidly (Fig. 1). "It's a brute force mechanism because our peptide pokes holes in the cell and then it dies, unlike most antibiotics, which act from inside the bacterial cell," said Gundersen. As a result, AMC-109 has a very rapid effect, which also means that cells have no time to defend themselves or to build up resistance.

AMC-109 has demonstrated efficacy against a wide range of organisms, including Gram-positive bacteria, Gram-negative bacteria and some fungi. It is also effective against antibiotic-resistant strains, such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE) and multi-resistant *Pseudomonas* isolates.

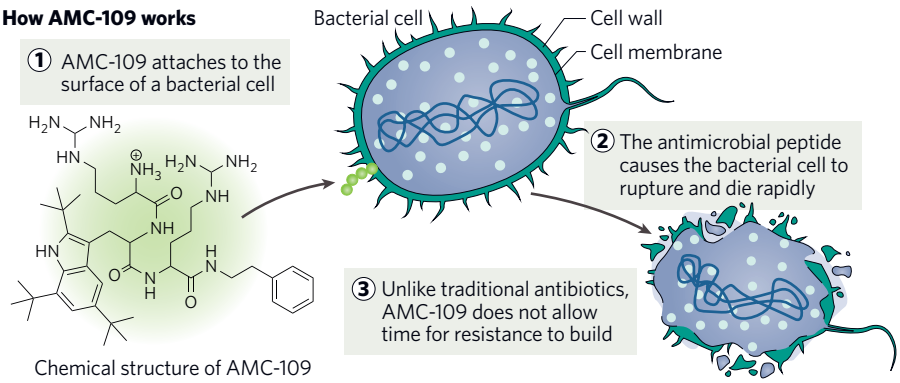

Fig. 1 | AMC-109 has rapid antibacterial action. Bacterial cells have no time to defend themselves or to build up resistance to AMC-109. In contrast, most antibiotics act more slowly from inside the cell, which allows more opportunities for resistance to develop.

The manufacture of AMC-109 has been optimized and represents a scalable current good manufacturing practice (cGMP) process with defined lead times.

Versatile coating technology

The AMC technology can cover a wide variety of shapes and surfaces, and is compatible with a range of different materials, including fibers, metals and different types of plastics in common use in the medical device industry.

It is also possible to control how tightly the peptide is attached to a medical device. For example, a fairly loose attachment of short duration may be required when using AMC-109 with a wound care product. "We have found that bandages containing AMC-109 work most effectively if the peptide can leak out into the wound itself to do its magic, so they can be designed to last until the bandage is due to be changed," said Gundersen.

For longer-term uses, such as orthopedic implants or synthetic heart valves, it is possible to couple AMC-109 to a surface more permanently through a cycloaddition ('Click') reaction. This single-step technology can be performed without harming either the solid support or the peptide. "As a result, the peptide is very tightly bonded chemically to the surface, which makes it much more resistant and prolongs the effect of coating the surface," said Gundersen.

Licensing opportunities

Amicoat sells commercial license rights to its AMC technology for use in specific products and offers a collaborative partnership throughout the product development and regulatory process. The company has already validated a strong demand for its antimicrobial coating technology from leading medical device manufacturers operating in an antimicrobial coating market of $5.5 billion that is growing quickly.

Each medical device using Amicoat's technology is required to go through a separate regulatory process. "Whether we collaborate on wound bandages, orthopedic implants or pacemakers, each product would have its own regulatory pathway that would need to be cleared," said Gundersen. "This is a very niche area and we have a lot of technology expertise to offer that can add value to our partners during the development stages." This includes a technical dossier for the active component, which has previously been tested in clinical studies.

Amicoat is committed to creating long-term value in an environmentally responsible manner for all its stakeholders—customers, the products they make and the patients who may enjoy better health by avoiding HAIs. "We truly believe our company can have a significant impact in improving and saving lives," said Gundersen.

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Sanofi Pasteur
www.sanofipasteur.com

SANOFI PASTEUR

Interested in partnering with Sanofi Pasteur?

Building on its history of successful collaborations, Sanofi Pasteur, the vaccines global business unit of Sanofi, is seeking partners with a common drive for excellence and pursuit of innovation.

Not only is Sanofi Pasteur at the forefront of conquering newly targeted diseases, but the company is also leading the way in expanding immunization across all age groups, including adolescents and the elderly. This leadership has translated into outstanding success in the industry.

Sanofi Pasteur is interested in partners who will share in the pursuit of innovation and the company's drive for excellence while becoming a part of its market success story. "We welcome the opportunity to evaluate technologies related to the development and production of human vaccines, both prophylactic and therapeutic, including vaccines for chronic infectious diseases," said Roman Chicz, global head of external research and development.

Sanofi Pasteur is improving global human health by the discovery, development, manufacture and supply of vaccines for the prevention and treatment of infectious diseases.

Sanofi Pasteur has a strong commitment to the establishment of research and development partnerships with major universities, research institutes, government agencies, biotechnology companies, non-government organizations and contract research organizations. The company's collaborations cover virtually all aspects of vaccine development, including early-stage research.

Patient receiving their annual flu shot.

Sanofi Pasteur is interested in potential partnering opportunities in the field of active and passive human immunization for infectious diseases, as well as technologies that support product development and industrial performance, including the following areas:

Vaccines, monoclonal antibodies and supporting technologies for prevention and treatment of infectious diseases
- Novel antigens and methods for antigen discovery and characterization
- Vaccine vectors suitable for nasal or oral use
- New ways to administer vaccines
- Carrier proteins and protein–polysaccharide conjugation methods or alternative technologies
- mRNA delivery technology

Agents to enhance vaccine immune responses
- Adjuvants and immunomodulators
- Vaccine vectors and delivery systems intended to enhance or modify immune responses
- Biological and immunological studies to further characterize adjuvants and immunomodulators

Characterization and assay of immune responses and disease markers
- Animal models of human diseases
- Biological markers for evaluating the efficacy of prophylactic or therapeutic interventions
- In vitro, ex vivo and 3D models of human tissues, including the immune system
- Epidemiological studies relevant to the use of vaccines and immunotherapeutics

Tools for improving vaccine and monoclonal antibody research, development and production
- Development and application of new technologies in the areas of genomics and proteomics
- Artificial intelligence, machine learning and machine vision
- Technology for the study of B cell immunology and immunosenescence
- Prokaryotic or eukaryotic cell lines for antigen production
- Fermentor and bioreactor technology
- Disposable systems
- Downstream processing, purification and aseptic filling processes
- Process automation
- Preservatives and stabilizers
- Nonionic detergents
- Anti-counterfeiting technology

Examples of current partnerships and technology investments include a protective monoclonal antibody against respiratory syncytial virus (RSV) infection in infants; vaccine candidates against RSV, herpes simplex virus, *Streptococcus pneumoniae* and broadly protective influenza; pediatric combination vaccines; large-scale cell culture-based virus production; adjuvants and immunomodulators; conjugate vaccine production; and vaccine delivery systems. In addition, the company partnered in 2018 with Translate Bio on their mRNA platform.

A company that partners with Sanofi Pasteur interacts with a multidisciplinary team with years of experience in working to ensure that partnerships are executed successfully and are nurtured for the mutual benefit of all parties.

This approach utilizes the value-added Sanofi Pasteur alliance management capability, which focuses on the relationship by the facilitation of open communication, trust, understanding and clear expectations across the project lifespan.

Combined with the technical competency of the alliance, this balance provides a well-rounded environment in which novel technologies can flourish. Currently, 100% of our preclinical portfolio and ~50% of our clinical portfolio has a partnering component.

Sanofi Pasteur welcomes information about new partnership opportunities. Each opportunity is carefully evaluated and reviewed by our dedicated team.

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TAXIS Pharmaceuticals, Inc.
www.taxispharma.com

Tackling resistance in multidrug-resistant bacterial infections

TAXIS Pharmaceuticals is developing first-in-class anti-resistance drugs to help re-engage widely prescribed but resistance-prone generic antibiotics to treat patients with multidrug-resistant infections. The company is actively looking to partner its lead assets with pharma and to in-license novel anti-resistance drug candidates for development.

TAXIS Pharmaceuticals, Inc. is a clinical stage company using its TAXISTENCE platform to develop anti-resistance drug candidates to enable the re-use of some of the most widely prescribed generic antibiotics against antibiotic-resistant bacteria, including the so-called ESKAPE pathogens—*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* spp. Antimicrobial resistance is considered one of the biggest global health threats facing humanity in the twenty-first century, jeopardizing the progress made over a century of medical innovation. For example, recent data suggest that up to one in seven patients hospitalized with COVID-19 develops a dangerous secondary bacterial infection, with 50% of those patients ultimately dying of bacterial infections.

TAXIS' strategy consists of addressing elemental forms of drug resistance by disrupting the bacterial cell wall architecture, including construction, maintenance and growth. The company's pipeline includes investigational, preclinical and clinical stage anti-resistance agents based on novel mechanisms of action that include efflux pump inhibition and modulation of the bacterial cell division process of cytokinesis.

"Our focus is on resuscitating the activity of generic antibiotics to facilitate access to inexpensive, life-saving medications in community settings across the globe," said Gregory G. Mario, President and CEO of TAXIS. "TAXIS' approach enables the use of reduced antibiotic doses without compromising pathogen kill rates and thus could help reduce or altogether eliminate the global risk of antibiotic resistance."

Generic antibiotics to work in MRSA

TAXIS' lead asset is TXA709, an oral anti-MRSA (methicillin-resistant *S. aureus*) agent that recently completed a first-in-human phase 1 clinical trial with no serious adverse events. TXA709 targets the filamenting temperature-sensitive mutant Z (FtsZ) bacterial cell division protein, blocking post-mitotic septum formation. TXA709 is being developed for synergistic use in combination with antibiotics rendered obsolete by bacterial resistance. A phase 1 combination study of low-dose TXA709 with the generic cephalosporin antibiotic cefdinir is scheduled to begin later in 2020. The study will provide key absorption, distribution, metabolism and excretion (ADME) as well as PK and toxicity data. The only oral MRSA therapy currently available is linezolid, but resistant strains have already emerged.

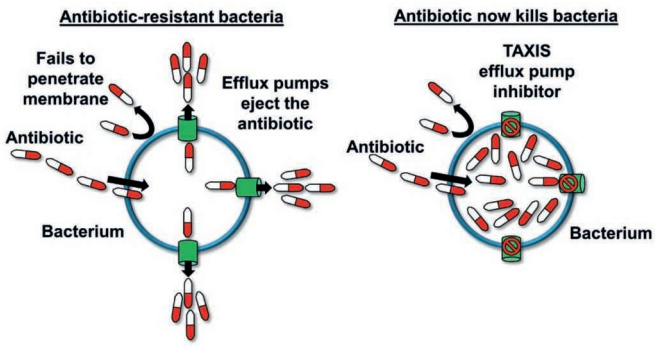

Fig. 1 | First-in-class anti-resistance drugs to help treat patients with multidrug-resistant infections. TAXIS has developed a strategy consisting of targeting bacterial efflux pumps, a family of multi-protein complexes that span the bacterial cell membranes and act like bilge pumps that flush antibiotics out of the cell.

The US Food and Drug Administration (FDA) has designated TXA709 a Qualified Infectious Disease Product (QIDP) under the Generating Antibiotics Incentives Now (GAIN) Act of 2012. The QIDP status grants eligibility for fast-track designation, priority review and 5 additional years of marketing exclusivity to encourage the development of new antimicrobial drugs to combat the rising threat of multidrug-resistant (MDR) bacteria.

TAXIS is evaluating the possibility of targeting FtsZ not only in Gram-positive bacteria but also in Gram-negative bacteria.

Targeting Gram-negative bacteria

MDR Gram-negative bacteria have been on the rise over the past decade, but few effective strategies to combat them have emerged.

TAXIS has developed a novel strategy consisting of targeting bacterial efflux pumps, a family of multi-protein complexes that span the bacterial cell membranes and act like bilge pumps that flush antibiotics out of the cell (Fig. 1). Indole carboxamide efflux pump inhibitors (EPIs) represent a new drug class designed to restore the efficacy of existing antibiotics against MDR Gram-negative bacteria. TAXIS' EPIs have been shown to restore the activity, potency and effectiveness of multiple classes of antibiotics including macrolides, cephalosporins, monobactams, antimycobacterials, tetracyclines, fluoroquinolones and sulfonamides. To date, this synergistic effect has been demonstrated in vitro with 28 approved and marketed antibiotics that no longer work in the clinical setting or require high doses to have any effect.

"We believe that advancement of our new anti-resistance drug candidates to combat MDR infections could result in a significant reduction in patient mortality with a substantial cost-effective societal benefit," said Mario.

Anti-resistance drug development

TAXIS' EPI program received a major boost earlier this year with a CARB-X award of $3.2 million, with potential for an additional $11.4 million, to support the company's project on extended-spectrum β-lactamase (ESBL)-producing *P. aeruginosa*. The company also partners with academic institutions to enable discovery and development at university-sponsored laboratories. Ongoing partnerships include Rutgers University, the Robert Wood Johnson Medical School, the ILSE at Kean College, University of Houston, and Princeton University.

According to Mario, "TAXIS has developed a unique portfolio of proprietary anti-resistance drug candidates designed to facilitate treatment of patients affected by antibiotic-resistant strains of bacteria. We offer a unique opportunity to potential partners interested in developing solutions to mitigate the rise in antibiotic resistance globally with safe and cost-effective solutions for patients."

The company is actively looking to partner its lead assets with pharma and to in-license novel anti-resistance drug candidates for development.

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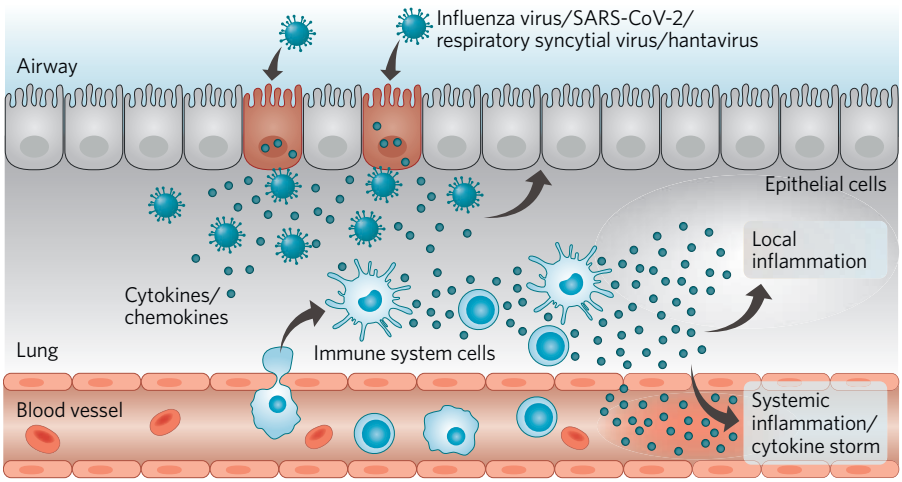
Atriva Therapeutics: transforming antiviral therapies

By acting directly on human cell machinery, Atriva Therapeutics' lead candidate antiviral ATR-002 combines several advantages over existing therapies and could combat respiratory diseases such as influenza and COVID-19.

With the world in the grip of a rapidly spreading pandemic caused by a lethal respiratory virus, the need for an effective antiviral treatment has never been greater. Coronavirus disease (COVID-19) is wreaking havoc around the world, devastating lives and economies. At the same time, the next influenza outbreak is a matter of when—not if, and will add to the healthcare and financial burden.

Unfortunately, no vaccines are available for COVID-19, and treatment options are very limited. Influenza vaccines can be only partially effective or not effective at all in some seasons. Moreover, currently approved antiviral therapies for influenza virus must be administered soon after the onset of symptoms (typically within 48 hours) and rapidly become ineffective as the virus mutates. "There is a dire need for a safe and efficacious therapy that avoids resistance, has a broader treatment window, and is suitable for high-risk groups," said Rainer Lichtenberger, co-founder and CEO of Atriva Therapeutics.



Viral multiplication and cytokine storm. ATR-002 addresses these effects, which often lead to severe progression of respiratory viral infections.

A novel approach

Atriva Therapeutics, a biopharmaceutical company based in Tübingen, Germany, is set to revolutionize the treatment of influenza, COVID-19 and other potentially life-threatening respiratory diseases. Conventional treatments are limited by a narrow window of therapeutic efficacy and, because they target viral proteins, show reduced efficacy once specific mutations appear in the virus. In contrast, Atriva's antiviral acts on the intracellular mechanism that is essential for viral propagation—an elegant approach that avoids resistance and broadens the time frame for application.

Influenza and some other RNA viruses rely on the Raf/MEK/ERK signaling pathway inside human cells to replicate. Atriva's lead candidate, ATR-002, is a small-molecule inhibitor of MEK, one of the key enzymes in the pathway, thereby preventing export of the viral genome protein complexes from the nucleus to the cytoplasm, in the case of influenza virus. Without these crucial building blocks, viral particles cannot be assembled and the virus can no longer propagate. This considerably controls the infection, ultimately reducing viral load in the body and allowing the adaptive immune system to clear the initial infection. Because the virus is not the target of the drug, it cannot escape the drug by mutation and thus, the risk of resistance developing is considerably lower.

In preclinical studies, the drug candidate rapidly blocked the Raf/MEK/ERK signaling pathway, significantly reducing influenza virus particle production in the body. Phase 1 data show that ATR-002 is safe and well tolerated and has a longer effective treatment window compared with standard-of-care therapies—a further notable benefit.

Calming the storm

Fatalities from COVID-19 and influenza are correlated with an overreaction of the body's immune system called a "cytokine storm". Although production of cytokines and chemokines is a normal part of the body's response to infections, certain cytokines can lead to inflammation. In some people, production of these pro-inflammatory cytokines can be excessive and damaging: cytokines and chemokines flood the body, attracting further immune cells to the site of infection, which in turn triggers production of more cytokines and chemokines—a vicious cycle of inflammation. In COVID-19 in particular, the site of infection is typically the lungs, with a cytokine storm leading to pneumonia and respiratory distress that in many cases is followed by organ failure and death.

This is where ATR-002 provides another significant advantage over standard treatments: the Raf/MEK/ERK pathway also regulates the gene expression of various cytokines and chemokines; blocking MEK, therefore, also prevents excessive cytokine/chemokine production. The MEK inhibitor ATR-002 reduces the overwhelming cytokine/chemokine response that is the cause of many fatalities. Thus, preventing hyper-inflammation is particularly important in the course of COVID-19.

ATR-002 has already shown promise to work in COVID-19 in preclinical studies, demonstrating both antiviral efficacy and immunomodulatory effects against SARS-CoV-2 in vitro. Given the great and urgent need for a safe and effective treatment for COVID-19, Atriva is prioritizing this indication for development; a phase 2 study in hospitalized patients with moderate COVID-19 is scheduled to begin in Q3 2020.

Potential in pandemics and beyond

ATR-002 has broad efficacy against RNA viruses that require the Raf/MEK/ERK signaling pathway for replication, including hantavirus and respiratory syncytial virus (RSV), which are also targets in the company's pipeline. Atriva welcomes new development partnerships with industry and academia for its proprietary candidate. "In COVID-19, influenza and other serious respiratory diseases, the death toll is driven by a combination of the viral infection and an overwhelming cytokine response," said Lichtenberger. "ATR-002, with its antiviral and immunomodulatory effects, has a double advantage over existing therapies and is uniquely positioned to benefit patients most at risk. This should help ease the burden on healthcare systems, particularly in pandemic environments."

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Dealmaking in 2020: navigating a new landscape

After a slow start to the year, dealmaking for the rest of 2020 is likely to be profoundly affected by the COVID-19 pandemic.

Credit: Guy Edwardes Photography/ Alamy Stock Photo

BioPharma Dealmakers

While many companies are facing exceptional challenges in finding partners and bringing deals to completion owing to the current coronavirus crisis, it has also triggered a wave of partnering as organizations rapidly sign deals to accelerate the development of vaccines, treatments and diagnostics to control the pandemic. In this feature, we explore mergers and acquisitions (M&A) and licensing activity in 2020 so far, based on data provided by Evaluate Ltd.

M&A trends

Before the COVID-19 pandemic took hold, M&A activity was already down compared with last year. There were 19 acquisitions announced in the first quarter of 2020 (Fig. 1a)—a few less in terms of numbers compared with the first quarter in 2019, but with less than half the total value, at just $6.2 billion compared with $16.5 billion. Indeed, Q1 has typically been the quarter with the highest-value deals of the corresponding year in the past 5 years (Fig. 1b), but the only two major M&As announced in this period in 2020 were Eli Lilly's $1.1 billion deal for the dermatology company Dermira in January and Gilead's $4.9 billion acquisition of the cancer immunotherapy biotech Forty Seven in early March. There have been two major M&As so far in the second quarter of the year, Menarini's $677 million acquisition of Stemline Therapeutics followed by Alexion Pharmaceuticals purchase of Portola Pharmaceuticals for $1.4 billion, but pending deals could be at risk of delayed closure, renegotiation or termination owing to COVID-19. M&A numbers and values could therefore drop substantially compared with recent years.

Licensing trends

Licensing activity in the first quarter of 2020 was also down, with 30 deals—the lowest by number in the past 5 years (Fig. 2a). With combined upfront payments worth $1.96 billion, it was also the lowest-value first quarter since 2017 (Fig. 2b).

The largest deal of the first quarter by upfront payment was Incyte's licensing of exclusive ex-US rights from MorphoSys to develop and commercialize tafasitamab, a CD19-targeted monoclonal antibody that has been filed for regulatory approval for the treatment of B cell malignancies (Table 1). In addition to a $750 million upfront payment, Incyte also made a $150 million equity investment in MorphoSys, and MorphoSys could receive up to $1.1 billion in milestone payments, plus tiered royalties.

Continuing the trend of recent years, there were also several other major deals in the oncology area at a much earlier development stage, with correspondingly smaller upfront payments (Table 1). Merck & Co.'s potential $2.55 billion deal with Taiho Pharmaceutical and Astex Pharmaceuticals focuses on the

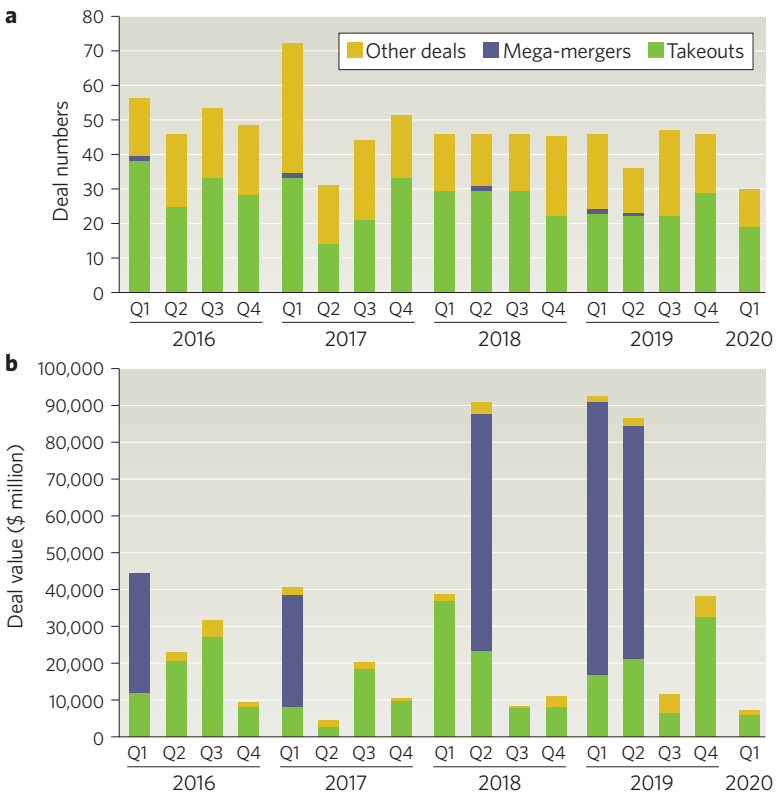

Fig. 1 | Trends in mergers and acquisitions by quarter since 2016. a, Mergers and acquisitions (M&A) count by deal announcement date. **b**, Cumulative M&A value by deal announcement date. The analysis includes company takeovers, as well as minority and majority stake purchases, acquisitions of business units, reverse mergers and options, which are aggregated in 'Other deals'. The numbers reflect only deals between dedicated drug makers; diagnostics and medtech transactions are excluded. Source: EvaluatePharma, April 2020.

Methodology box

This analysis is based on data extracted from EvaluatePharma in April 2020, and reflects licensing and M&A transactions announced with disclosed deal values. M&A deals data include company takeouts, minority and majority stake purchases, acquisitions of business units, reverse mergers and options. Licensing deals data analyzes in-licensing transactions only. All data reflect deals between dedicated drug makers only—diagnostics and medtech transactions are excluded.

development of small-molecule inhibitors against several drug targets, including the *KRAS* oncogene, which is currently one of the hottest anticancer targets. Genentech entered into a potential $1.7 billion collaboration with Bicycle Therapeutics to discover and develop bicyclic drug candidates for immuno-oncology applications. And finally, in the only major deal in the second quarter, Johnson & Johnson's Janssen Biotech announced a potential $3 billion partnership with Fate Therapeutics to develop cancer immunotherapies derived from induced pluripotent stem cells.

Pandemic spurs partnering

Although dealmaking overall has been subdued in 2020, the coronavirus pandemic has spurred a flurry of collaborations at a record pace, driven by the urgent need for treatments and vaccines. In addition to multiple vaccine partnerships involving major pharma companies, such as Sanofi, GSK, Johnson & Johnson, Pfizer and AstraZeneca (see the feature on pB18), many collaborations have also been established around potential treatment options. Vir Biotechnology has been one of the most prolific dealmakers following its discovery of two antibodies targeting the virus's spike protein, signing deals with WuXi, Alnylam, Xencor, the NIH, Biogen and GSK for various antibodies and RNA interference (RNAi) therapeutics, as well as vaccines. Other notable coronavirus-related business development activities focus on plasma from patients who have recovered from COVID-19, including deals between XBiotech and BioBridge, and Amgen and Adaptive that seek to identify neutralizing antibodies to develop as a treatment. Over the next few months, the pandemic's full effects on dealmaking and the industry as a whole will become clearer.

Acknowledgements

The authors would like to acknowledge Evaluate Ltd. for providing both the M&A and licensing data. COVID-19 XWG-03

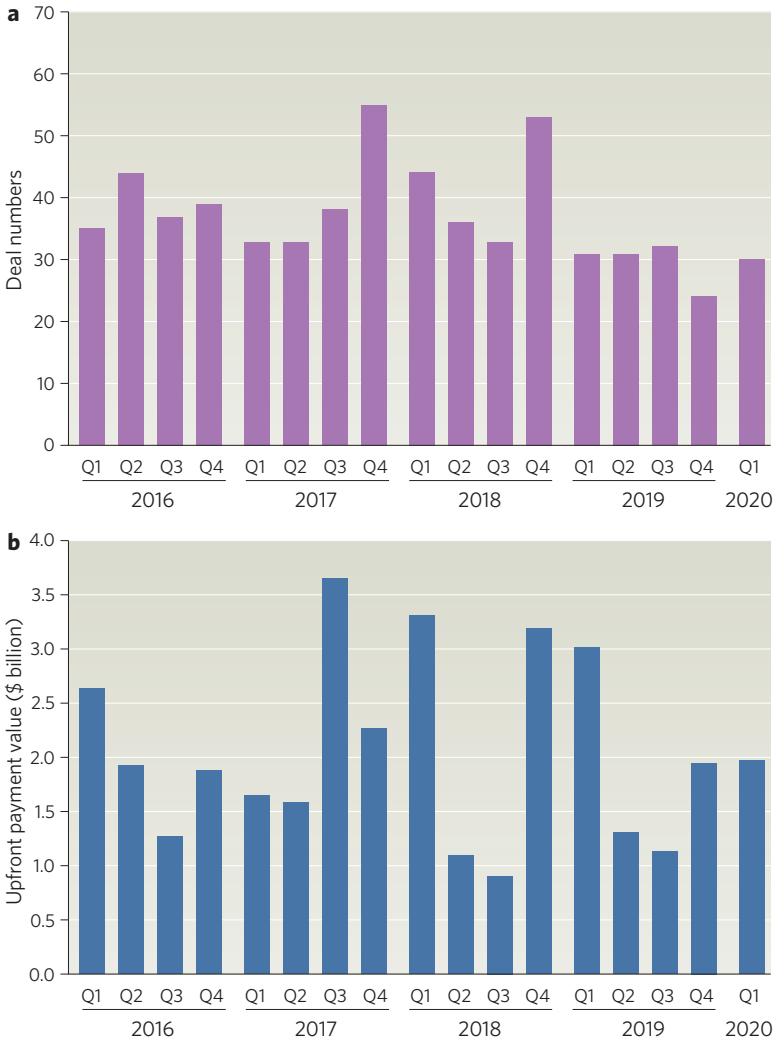

Fig. 2 | Licensing deals by quarter since 2016. a, Licensing deal numbers by upfront payments. **b**, Upfront payment values of licensing deals. The numbers reflect only deals with disclosed values between dedicated drug makers; diagnostics and medtech transactions are excluded. Source: EvaluatePharma, April 2020.

Table 1 | Highest value partnering deals of the year so far

Deal focus	Date	Company	Partnering company	Development status	Upfront payment ($ million)	Deal value ($ million)
Janssen Biotech (part of Johnson & Johnson) and Fate Therapeutics announce a collaboration to develop T cell cancer immunotherapies based on induced pluripotent stem cells	2 April 2020	Johnson & Johnson	Fate Therapeutics	Research project	–	3,000
Merck signs licensing deal with Taiho Pharmaceutical and Astex Pharmaceuticals (a subsidiary of Otsuka Pharmaceuticals) to develop small-molecule inhibitors of cancer targets, including *KRAS*	6 January 2020	Merck & Co	Otsuka Holdings	Preclinical	50	2,550
Biogen licenses rights to develop and commercialize gene regulation therapies identified by Sangamo Therapeutics for neurological diseases such as Alzheimer disease and Parkinson disease	27 February 2020	Biogen	Sangamo Therapeutics	Preclinical/ research project	350	2,370
Incyte licenses ex-US development and commercialization rights to MorphoSys' tafasitamab, a CD19-targeted monoclonal antibody that has been filed for regulatory approval for the treatment of B cell malignancies	13 January 2020	Incyte	Morphosys	Filed	750	2,000
Genentech (a subsidiary of Roche) partners with Bicycle Therapeutics to develop and commercialize immunotherapies based on bicyclic molecules against a number of targets	25 February 2020	Roche	Bicycle Therapeutics	Research project	30	1,700

The data cut-off date was 30 April 2020. IND, investigational new drug. Source EvaluatePharma, April 2020.

D&D PharmaTech
www.ddpharmatech.com

Addressing critical unmet healthcare needs

D&D Pharmatech funds the development of innovative therapeutic and diagnostic solutions to address critical unmet medical needs. D&D subsidiary Theraly Fibrosis is developing a novel treatment for chronic pancreatitis and other fibrotic indications, TLY012. Neuraly, another D&D subsidiary, recently launched a phase 2 study in Parkinson disease.

Clinical-stage global biotech company D&D Pharmatech was founded with a mission to drive the development of novel medicines through disease-specific subsidiary companies founded by a top-tier medical research faculty. This corporate structure allows D&D Pharmatech to accelerate the translation of cutting-edge research into lifesaving therapeutic products for patients.

D&D Pharmatech has assembled a pipeline of clinical-stage investigational medicines through licensing agreements with leading academic research centers. Since its founding in 2014, D&D Pharmatech has established four subsidiaries in the USA—Theraly Fibrosis, Inc., Neuraly, Inc., Precision Molecular, Inc. and Valted Seq, Inc.—and is continually looking for new opportunities to source innovative solutions.

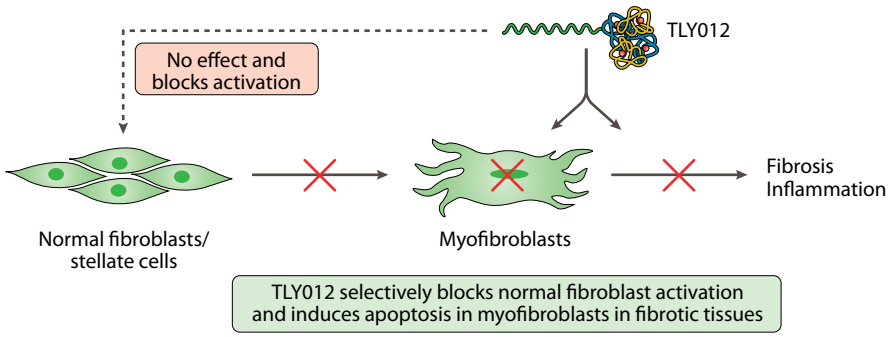

Fig. 1 | Blazing a TRAIL in fibrotic disease. Theraly's lead product candidate is TLY012, a recombinant version of the human TRAIL protein that selectively targets myofibroblasts (MFBs) involved in fibrosis. Reversing fibrosis has the potential to cure fibrotic diseases such as systemic sclerosis, liver fibrosis or cirrhosis.

A new TRAIL for fibrotic disease

Theraly Fibrosis' lead development program centers on human tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL). TRAIL helps remove myofibroblasts—the key contributors to fibrotic disease—and blocks de novo conversion of normal fibroblasts into those driving fibrosis regardless of tissue type[1] (Fig. 1). Because of this, TLY012, Theraly's proprietary version of TRAIL, has the potential to be a first-in-class treatment for a range of fibrotic diseases, including chronic pancreatitis, non-alcoholic steatohepatitis (NASH), liver fibrosis, liver cirrhosis and systemic sclerosis.

TRAIL has been studied as a therapeutic over the past 20 years, primarily as a potential treatment for cancer. However, soluble recombinant TRAIL has a short half-life and is not very stable. TLY012 is more stable and has a greatly increased circulating half-life. The company is first developing TLY012 for chronic pancreatitis, an incurable fibrotic disease characterized by chronic pain and progressive fibrosis that damages the pancreas and results in the loss of endocrine and exocrine function. In September 2019, TLY012 obtained orphan drug designation from the US Food and Drug Administration for the treatment of chronic pancreatitis, and Theraly is planning to initiate phase 1 clinical studies in late 2020.

Theraly's goal is to further develop TLY012 as a therapy for other major fibrotic diseases. The market for liver fibrosis—the largest target market for TLY012—alone is growing at high double-digit annual rates globally. "We are planning to carry TLY012 through end of phase 2 and are seeking an option-based partnership to support this effort," said Joshua Yang, head of business development and corporate strategy. "In addition, we are pursuing parallel clinical development for multiple indications of TLY012."

A total care system for neurodegenerative diseases

Neuraly, Precision Molecular and Valted Seq are each tackling neurodegenerative diseases by addressing a major need in the field: developing novel therapeutic agents, advancing powerful imaging platforms and analyzing genetic data to improve diagnosis and disease monitoring, respectively.

Neuraly's lead compound is NLY01, a potent, long-acting glucagon-like peptide 1 receptor (GLP1R) agonist. NLY01 inhibits activation of microglial cells in the brain, limiting neuroinflammation and neurodegeneration in Parkinson disease (PD)[2] and Alzheimer disease (AD) and potentially other diseases. Neuraly started a phase 2 proof-of-concept clinical trial with NLY01 in PD in February 2020 and is planning a phase 2 in AD in Q4 2020.

Precision Molecular is advancing four clinical stage imaging agents and one investigational new drug (IND)-enabling PET imaging agent for early detection and management of neuroinflammation in AD and PD. Precision Molecular's imaging agent PMI04 targets proteins expressed in activated microglia and proteins involved in neuroinflammation, providing a non-invasive approach to quantifying neuroinflammation[3]. These products are ideal companion diagnostics for medications such as NLY01 and as independent tests to help identify patients with early-stage or asymptomatic disease. The company received an investment from the Alzheimer's Drug Discovery Foundation and researchers who are working on the agents received additional funding from the Michael J. Fox Foundation.

Valted Seq is developing the world's largest collection of single-cell information derived from diseased post-mortem brain tissues. This unprecedented collection of big data related to neuroinflammation will be invaluable for identifying biomarkers for targeted therapy and early diagnosis of neurodegenerative diseases. According to Seulki Lee, Founder and Chairman of D&D Pharmatech, "Precision Molecular and Valted Seq will play critical roles in the development of diagnostic technologies to be used together with Neuraly's pipeline and other innovative technologies. The resulting synergy supports the companies' paradigm of total care, 'early diagnosis—early treatment'."

Flexible partnering for innovations

Following a successful Series B financing round worth $137.1 million, the clinical programs of D&D Pharmatech's companies are completely funded to date at this point. The company has more than 70 employees and an experienced R&D team leading multiple clinical studies and identifying new drug candidates to expand its pipeline.

"We are constantly evaluating new candidates for development and business collaborations to continue fulfilling our mission of developing innovative drugs to address critical unmet medical needs," said Yang.

1. Park, J.-S. et al. *Nat. Commun.* **10**, 1128 (2019).
2. Yun, S. P. et al. *Nat. Med.* **24**, 931 (2018).
3. Horti, A. G. et al. *Proc. Natl Acad. Sci. USA* **116**, 1686 (2019).

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nference: augmenting intelligence, transforming health care

Making the world's biomedical knowledge computable.

Speaking in 2019, Bill Gates said that if he were beginning his career today he would "start an [artificial intelligence] company whose goal would be to teach computers how to read, so that they can absorb and understand all the written knowledge of the world."

This is one of the key goals that nference has been pursuing for biomedical knowledge since it was founded in 2013. Headquartered in Cambridge, Massachusetts, nference has grown rapidly in the past 2 years, tripling its workforce to more than 150 scientists and engineers with advanced degrees from world-leading biomedical and computer science institutions, including the Massachusetts Institute of Technology and Harvard Medical School. Today nference has offices in Bangalore, India; Toronto, Canada; and Rochester, Minnesota.

nference operates at the convergence of three growing trends: the explosion of biological knowledge in the 'multi-omics' era, the coming of age of electronic health records and new developments in deep-learning neural networks. nference is uniquely positioned to generate new insights into health care by occupying the sweet spot that exists at the intersection of basic biology, clinical care and computer science.

Unlocking biomedical knowledge

The ever-increasing growth of biological knowledge from genomics, single-cell RNA sequencing, proteomics, metabolomics and all the other strands of the multi-omics era are yielding deep insights into disease processes and pathology. Making the best use of this enormous quantity of data has, however, been hampered by the fact that these data sets often sit in distinct silos, and the expert know-how needed to leverage insights from multi-omics data resides in a few specialized labs.

At the same time, a vast amount of valuable but untapped biomedical knowledge is encoded in electronic health records. A small proportion of this knowledge is represented by structured data, such as the International Classification of Disease (ICD) codes, which provide important insights into the clinical status of patients. A drawback of these structured data is that they use, by necessity, a very constrained and inflexible vocabulary that is frequently unable to capture crucial details about the context and specific details of a patient's journey in the healthcare system. In many ways, trying to capture the complexity of a patient's clinical experience with such structured data is akin to trying to describe the rich details of someone's biography in a spreadsheet with a highly confined choice of words and clichés that have been generalized for the whole population.

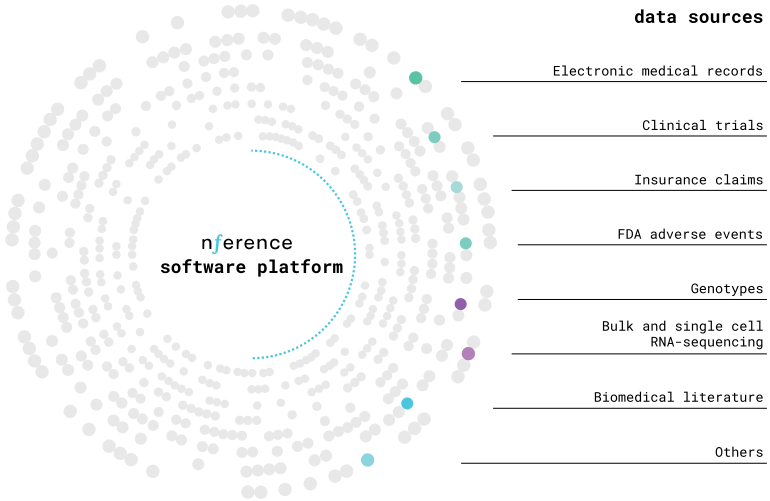

Fig. 1 | Pieces of the platform. A wide variety of data sources contribute to the nference technology platform. The machine-learning analysis derived from the collection of these sources helps to unlock and extract the knowledge and value from unstructured health records.

Alongside the structured data that reside in electronic health records sits a much greater volume of unstructured information in the form of physician notes. This information, written by physicians to be read by other physicians, contains fine-grained contextual and patient-specific details about health and disease over time, and comprises up to 90% of veritable biomedical information in the electronic health records. Up until now, this rich resource has been largely untapped, except when individual physicians have consulted the notes in the course of their clinical care for patients.

Extracting and curating valuable health data

nference is seeking to revolutionize the value of electronic health records and turn this unstructured data into knowledge that can be used widely by the biomedical and health-care communities. To achieve this goal, nference is using deep-learning neural networks to extract and curate insights from the wealth of unstructured or semi-structured data currently sitting silent in electronic health records. This is a golden age of computer science, and artificial intelligence (AI) driven by machine learning and neural networks is set to seep into every aspect of our personal and professional lives, from self-driving cars, smart homes and facial recognition to AI-driven financial services, AI-regulated energy sectors and, in nference's vision, health care.

The knowledge extracted from unstructured health records is valuable by itself, but gains even more worth when married to insights and inferences that emerge from the machine-learning analysis of other forms of unstructured data. These include the output of multi-omics efforts, details of clinical-trial protocols, imaging data such as radiology, as well as more than 100 million biomedical documents from diverse sources such as PubMed, clinical trial records, US Securities and Exchange Commission (SEC) filings, grants, preprints, patents, company websites and the broader media. These sources can be additionally buttressed by numerous structured databases, such as lab tests, vitals and the US Food and Drug Administration (FDA) adverse event reporting system (Fig. 1).

Although machine learning and neural networks are central to the nference technology platform, the result is not AI as some understand it. Instead, nference dubs their approach 'augmented intelligence', an alternative conceptualization of AI that focuses on its assistive role and emphasizes the fact that cognitive technology is designed to enhance human intelligence rather than replace it. The notion of augmented intelligence reinforces the role that expert human intelligence plays, particularly the curiosity that drives many salient research questions when developing thoughtful machine-learning and deep-learning models.

Such augmented intelligence, nference believes, will help rapidly pressure-test hypotheses to weed out the vast majority of false positives and false negatives in putative relationships via intense triangulation across diverse data sets.

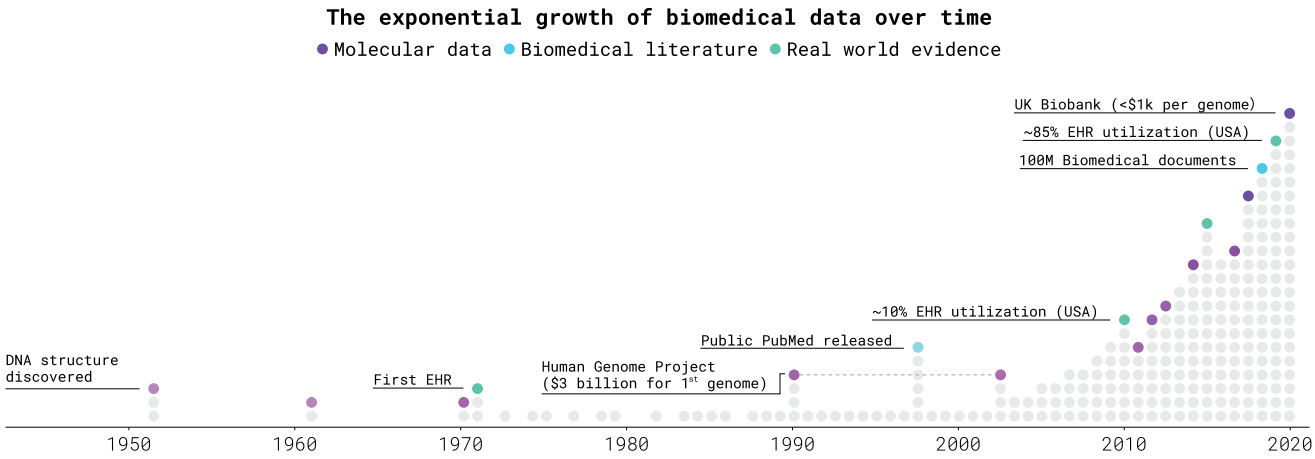

Fig. 2 | Timeline charting the growth of biomedical data. Since the discovery of DNA in the early 1950s to the sequencing of the human genome in the 1990s, the quantity of global biomedical data has rapidly grown.

This distinctive approach, which blends the best of human scientists' training and wisdom with the ongoing renaissance in deep-learning and unsupervised neural networks, has the potential to aid all aspects of health care, including drug discovery, clinical research, clinical-trial operations, life cycle management and clinical care.

Partnering with the Mayo Clinic

In a major step forward toward fulfilling the company's vision, *n*ference recently received $60 million in Series B financing that included a significant strategic investment from the Mayo Clinic. The strategic partnership with Mayo Clinic was established to transform health care by applying the distinctive *n*ference technologies to making nearly 150 years' worth of Mayo's proprietary knowledge bases computable and actionable for researchers, drug hunters, physicians and patients.

Mayo has digitized more than 9 million complete electronic health records containing huge amounts of unstructured knowledge, with nearly 25 million pathology slides in their archives and patient-derived biospecimens. These resources provide another crucial link for connecting multi-omics data and deep pathological inferences to the context-rich, real-world, de-identified clinical trajectories of patients. *n*ference is already de-identifying and gearing up to analyze the structured data residing in the de-identified health records, while simultaneously innovating technologies that overcome the scientific challenges that have prevented other companies from augmenting the human curation of rich unstructured knowledge through machine intelligence.

The strategic partnership between Mayo and *n*ference constitutes Mayo's Clinical Data Analytics Platform (CDAP) initiative, which has been established with Google as a cloud provider to house the de-identified data securely. The Mayo CDAP initiative features a distinctive federated architecture that has the potential to dramatically improve biomedical research and health-care delivery by bringing sophisticated digital technologies and augmented intelligence models from *n*ference and its partners into the secure cloud framework.

In the current era of almost universal use of social media, privacy issues have rightfully emerged as a major concern among citizens and regulators. *n*ference puts patient privacy first in all its efforts. In the CDAP initiative, de-identified patient data reside fully within Mayo's span of control and do not leave their secure cloud framework. In addition to ensuring that even the anonymized patient data do not get into the hands of others, this secure federated learning model brings machine intelligence to bear where the data truly belong—the care provider's infrastructure.

> **"A holistic, machine-learning platform that synthesizes deep biological knowledge with insights drawn from large cohorts of fully de-identified health records is key to creating new life-saving therapies and the most effective clinical care solutions**
>
> Venky Soundararajan, Co-founder and CSO, *n*ference

Taking advantage of the explosion in biomedical data presents great challenges (Fig. 2), but the payoffs for stakeholders across the entire spectrum of health care are enormous. For clinicians, augmented intelligence through machine learning could dramatically improve patient care. Today, physicians can draw on the clinical insights of a small number of colleagues with whom they interact in their day-to-day work or in collaborations that draw on a limited number of manually de-identified patient health records. With ground-breaking automated de-identification technology from *n*ference, combined with the augmented curation and triangulation technologies that *n*ference has developed, physicians and practitioners in the near future will be able to draw on the collective wisdom of entire institutions such as the Mayo Clinic. Patients will be much more likely to receive the best standard of care, and the most appropriate therapies for their personalized medical needs.

Opportunities for biopharma

For the biopharmaceutical sector, the opportunities created by augmented intelligence applied to the unstructured data created by multi-omics and many other diverse data sources are similarly profound. The impact will be felt at every stage of the R&D chain, from identifying new drug targets and the design of preclinical studies that predict drug efficacy and safety, as well as translational medicine for patient segmentation based on biomarkers, to the design of clinical-trial protocols that reduce protocol complexity and amplify appropriate patient recruitment as part of clinical-trial operations. But the impact of data-science solutions does not stop there, and will contribute to the entire life cycle management of drugs, informing strategies for post-marketing surveillance and label expansions, decisions about drug repurposing for addressing unmet clinical need and business development strategies based on intense market segmentation and competitive landscaping.

*n*ference believes that the convergence of the three strands of multi-omics, electronic health records and computer science, in this era of exponential knowledge growth across public and proprietary domains, is the wave of the future. "The explosion of digital biomedical information has the power to revolutionize drug development and health-care delivery. We believe that a holistic, machine-learning platform that synthesizes deep biological knowledge with insights drawn from large cohorts of fully de-identified health records is key to creating new life-saving therapies and the most effective clinical care solutions," said Venky Soundararajan, co-founder and CSO of *n*ference.

*n*ference is advancing new strategic collaborations with biopharmaceutical companies operating at all stages, from early R&D to clinical development. *n*ference is also fostering deep strategic partnerships with leading academic medical centers to help them de-identify and synthesize the vast stores of clinical knowledge that currently remain largely unviable for biopharma research and clinical care at a meaningful scale that drives significant patient benefit.

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Noveome Biotherapeutics, Inc.
noveome.com

ST266—a next-generation anti-inflammatory and neuroprotective platform biologic

Noveome Biotherapeutics, Inc. is developing a new class of biologic consisting of the secretome from a novel population of cells derived from the amnion. The biological factors secreted by these cells have unique anti-inflammatory and neuroprotective effects. Presently, the company is looking for partners to drive clinical drug development of its lead product, ST266, in ophthalmic indications.

Noveome Biotherapeutics, Inc. is a clinical-stage biopharmaceutical company focused on developing next-generation biologics for the promotion and restoration of cellular integrity of diseased or damaged tissues.

ST266 is a first-of-its-kind, multi-targeted, non-cellular platform biologic with the potential to improve patients' outcomes across a range of challenging diseases and conditions in ophthalmology, neurology, dermatology and others. Many of these conditions currently have no or limited therapeutic options, in part because they are often too complex to be treated with traditional 'one-drug, one-target' therapies.

The components of ST266 are secreted by a novel population of cells generated by a proprietary method of culturing selected amnion-derived epithelial cells collected from full-term placentas normally discarded after birth. The cells produce many of the biological factors found in amniotic fluid that may be responsible for the remarkable healing capabilities and lack of scarring observed following in-utero fetal surgery.

The company is evaluating ST266 in multiple indications including ophthalmic conditions such as optic neuritis, glaucoma and persistent corneal epithelial defects (PEDs). Noveome uses targeted intranasal delivery of ST266 to bypass the blood–brain barrier (BBB), clearing a major hurdle to reach the optic nerve directly for treatment (Fig. 1). The company has an ongoing phase 1 trial to assess the safety of intranasal ST266 and an ongoing phase 2 trial in which ST266 is applied topically to treat PEDs.

Noveome is now looking for potential corporate partners interested in the clinical development and eventual commercialization of ST266 for optic neuritis and glaucoma.

According to Larry Brown, CSO and executive vice-president of R&D at Noveome, "ST266 provides a potentially revolutionary new way of treating ophthalmic conditions by targeting the optic nerve directly rather than just managing risk factors and symptoms such as elevated ocular pressure. We are first focusing on optic neuritis to prove the concept, but we believe the greatest opportunity will be in the treatment of glaucoma."

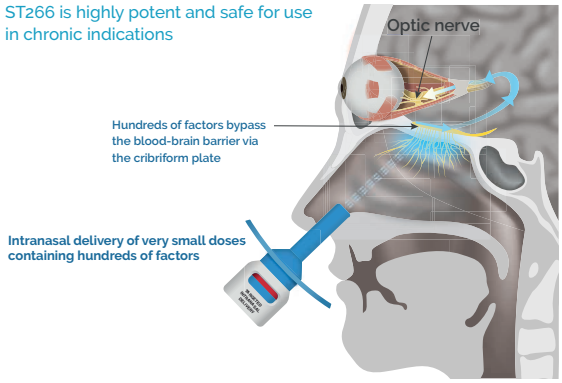

Fig. 1 | Next-generation multifactorial biologic for optic nerve and brain conditions. The non-cellular, multi-target platform biologic, ST266, stimulates anti-inflammatory and neuroprotective pathways. ST266 is delivered intranasally directly to the optic nerve and the brain, thereby bypassing the blood–brain barrier.

ST266—groundbreaking potential

Normal tissue healing is a complex process that requires a combination of growth factors, cytokines and extracellular matrix components. In the 1970s, scarless, regenerative wound healing was first observed in the fetal environment, and this phenomenon was attributed to growth factors and cytokines secreted by the amnion epithelial cell layer of the placenta.

Noveome was founded to translate this observation into a novel therapeutic solution. The company has developed a proprietary culture method to create amnion-derived multipotent progenitor (AMP) cells as a primary source of the complex matrix of secreted biological factors—the secretome.

Reduction of inflammation, vision recovery, and retinal ganglion cell and myelin preservation capabilities of ST266 have been demonstrated in an animal model of optic neuritis in multiple sclerosis[1] and an optic nerve crush traumatic injury model[2]. Lot-to-lot reproducibility of ST266 is ensured by the measurement of and conformance to specifications for a representative subset of factors in the secretome.

Noveome uses noninvasive intranasal administration to enable delivery of ST266 to the olfactory nerve, optic nerve and brain and thus target the neuroprotective effects of ST266 to the central nervous system. In preclinical studies with rodents and non-human primates, the highest concentrations of ST266 were observed in the optic nerve, leading Noveome to focus initially on ophthalmic indications. Backed by positive good laboratory practice (GLP), safety and toxicology studies using the intranasal device to deliver ST266, Noveome submitted an investigational new drug (IND) application to the US Food and Drug Administration in August 2019 and obtained a 'safe to proceed' evaluation from the agency.

"This is a real opportunity to save the optic nerve, and ST266 should be of great interest to companies operating in the glaucoma space who are looking at ways in which to treat the optic nerve directly," said Brown.

A broad collaborative spectrum

ST266 is being evaluated in several indications. Beyond identifying corporate partners for the development and commercialization of ST266 for optic neuritis, glaucoma or age-related macular degeneration, Noveome is also exploring the use of ST266 for other indications, such as chronic traumatic encephalopathy, polytrauma and necrotizing enterocolitis. For these other applications, Noveome is seeking partners to drive further development.

"Noveome's focus is on intranasal delivery of ST266 and its potential to treat conditions such as optic neuritis and glaucoma," said Brown. "But we are also looking for partners who might be interested in the preclinical development of other applications of ST266 that might allow us to address other pressing global health challenges."

Noveome also recently launched a program to evaluate ST266 as a potential treatment of the severe inflammatory cytokine storm response frequently observed in the lungs of patients with COVID-19.

1. Khan, R. S. *Sci. Rep.* **7**, 41768 (2017).
2. Grinblat, G. A. *Invest. Ophthalmol. Vis. Sci.* **59**, 2370–2477 (2018).

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Panorama Medicine
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Advanced drug discovery for transcriptome-associated diseases

Panorama Medicine has built a combined genomics and advanced computational analysis platform to develop therapies for diseases treatable through transcriptome modulation. The company is looking to partner its therapeutic solutions through licensing options, or to collaborate on custom screening projects.

Panorama Medicine is an RNA genomics- and computing-powered drug discovery company that develops therapeutic interventions for a range of common and rare diseases associated with messenger RNA (mRNA) abnormalities. Splicing of pre-mRNA into mature mRNA is an essential step for gene expression in higher eukaryotes. Errors in this process generate defective mRNAs that can result in dysfunctional proteins or proteins that are missing altogether affecting cellular function and potentially causing disease. The company's proprietary transcriptome-wide drug screening platform Pan-ACEA (Panorama's Automated Compound Effect Analyzer) identifies drugs to treat such RNA splicing-associated diseases as well as other diseases treatable through modulation of the transcriptome.

"Panorama's technology comprehensively profiles global transcriptomic responses to small-molecule compounds and matches the effects to Panorama's curated disease database," said Mingfu Zhu, co-founder and CEO of Panorama. "This strategy efficiently identifies the compound's potential to treat numerous diseases."

Panorama offers opportunities for licensing partnerships to further develop therapeutic leads discovered through Pan-ACEA and for building collaborations around custom screens and compound evaluations.

Building a Pan-ACEA

Pan-ACEA leverages proprietary disease databases to identify lead compounds from a library of carefully selected compounds that induce changes in RNA splicing and/or expression. This strategy allows Panorama to identify potentially de-risked compounds—all compounds in Panorama's library have been deemed safe in phase 2 studies but were terminated in later-phase studies owing to lack of efficacy for the original indications—that could treat specific transcriptome-associated diseases (Fig. 1). Pan-ACEA has the capacity to deliver drug candidates for multiple diseases simultaneously as well as to identify structurally diverse candidates for a particular condition at the same time.

Pan-ACEA can screen compounds for different kinds of transcriptomic errors, including aberrant splicing, which can be treated through modulating the balance between correct and aberrant mRNAs; insufficiently expressed transcripts, which can be treated through targeted modulation of expression; and some undisclosed directions that are under active development. Panorama has ongoing programs in all three modalities.

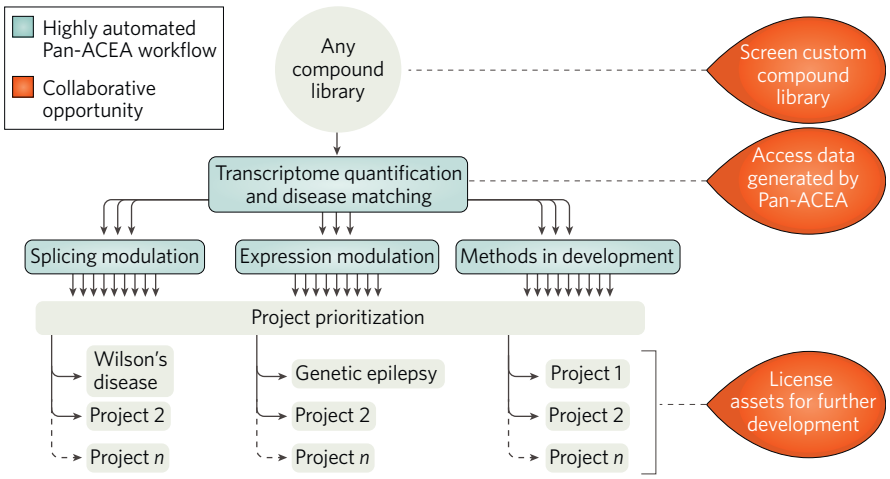

Fig. 1 | Panorama Medicine's Pan-ACEA platform. Panorama leverages genomics and computing to identify de-risked lead compounds that could help treat specific transcriptome-associated diseases.

Wilson's disease is a rare disease caused by aberrant splicing of the ATPase copper transporting β (*ATP7B*) mRNA, which results in accumulation of copper by the body and debilitating symptoms such as swelling, fatigue, abdominal pain, and uncontrolled or poorly coordinated movements. Panorama has identified a compound, Pano-002, that reduces exon skipping caused by a missense mutation and an intronic mutation associated with the disease.

Another lead program at Panorama focuses on a form of genetic epilepsy caused by reduced expression of a synaptic protein. The company has identified two compounds, Pano-013 and Pano-066, which promote increased expression of the gene.

According to Zhu, "Pan-ACEA is a disease agnostic platform that is ideally suited to address any transcriptome-related disease rapidly and with high accuracy. This is of particular relevance when trying to advance first-in-class therapeutic options for numerous rare diseases."

Flexible partnering opportunities

Panorama has built a drug discovery platform that lends itself to a variety of partnering opportunities. The company's main thrust is in developing de-risked therapeutic leads primarily for rare, transcriptome-associated diseases. With a number of leads already in its pipeline for select diseases amenable to splicing modulation or modulation of gene expression, Panorama is the partner of choice for companies looking to in-license de-risked lead candidates for conditions triggered by aberrant RNA processing and expression.

Panorama is further seeking collaborations with potential partners interested in mining the company's unique and comprehensive transcriptome-associated disease database to access compound-, disease- or transcriptome-specific information. Such projects could lead to joint development programs and other collaborations.

Finally, Panorama also offers the possibility to interested parties to use its Pan-ACEA platform to screen alternative compound collections to identify other potentially addressable targets in transcriptome-associated diseases.

"Our platform provides us with great flexibility in terms of collaborating with interested external parties," said Zhu. "While our primary goal is to develop new therapies in-house to advance the treatment of transcriptome-associated diseases, we are also eager to share the treasure trove of deep disease data and broad screening capabilities we have to complement external efforts leading to the same goal."

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Henlius Biotech
www.henlius.com

Henlius: using a fully integrated platform to advance high-quality, affordable biologics

With its dynamic end-to-end in-house capabilities, Henlius has developed a unique pipeline of cancer and autoimmune drugs, including HLX01, a biosimilar version of MabThera. The company is now exploring the creation of further biosimilars and immuno-oncology combination therapies.

Shanghai Henlius Biotech, Inc. has progressed quickly since it began operating in 2010. Today, Henlius is a fully integrated biopharmaceutical company with dozens of clinical-phase candidates racing to join its biosimilar version of MabThera on the market.

Fosun Pharma and a team of overseas scientists founded Henlius to offer high-quality, affordable and innovative medicines to patients worldwide. Working out of the headquarters in Shanghai and R&D centers in Taipei and California, Henlius quickly moved 14 products into clinical development and won approval for the first biosimilar in China.

Henlius's rapid growth is built on a fully integrated platform that gives it innovative in-house capabilities across the entire biologics value chain, including high-titer cell line, proprietary cell culture production and continuous manufacturing process at a good manufacturing practice (GMP)-certified production plant capable of handling commercial production of multiple products.

Building a broad biologics pipeline

Henlius has used its platform to build and advance a diversified pipeline of cancer and autoimmune drugs. The power of this approach is evidenced by HLX01, Henlius's biosimilar version of MabThera. In February 2019, the Chinese regulator approved HLX01 for three indications in non-Hodgkin's lymphoma (NHL), making it the first biosimilar to come to market in the country.

The Chinese approval of HLX01 in NHL is a launchpad for Henlius. With commercial sales of HLX01 underway, Henlius is conducting a phase 3 rheumatoid arthritis trial to expand the Chinese label while bringing the MabThera copy and other products to global markets.

HLX02 exemplifies the desire of Henlius to expand globally. This biosimilar version of Herceptin (trastuzumab) was the first Chinese-developed, off-patent biologic to be approved for study in humans outside the country. In June 2019, the European regulator accepted for review the submission of the application for approval of HLX02, setting it up to potentially become the first Chinese-developed biosimilar to come to market in the European Union (Fig. 1).

Henlius's ambitions extend beyond providing affordable versions of existing therapeutic options. The biotech also offers patients new, better treatments.

In some cases, Henlius is pursuing that goal by developing biosimilars in new indications, for example, by aiming to bring HLX04, a biosimilar version of Avastin (bevacizumab), to Chinese patients with wet age-related macular degeneration or diabetic retinopathy for the first time. Additionally, Henlius is working on wholly new molecules by applying its drug discovery capabilities to targets with huge unmet medical needs.

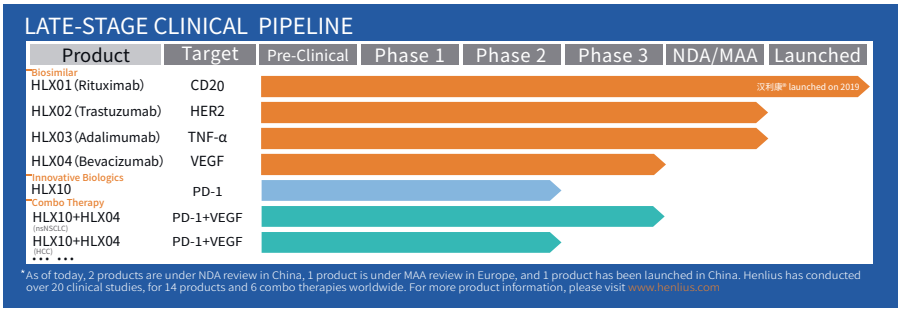

Fig. 1 | The Henlius late-stage clinical pipeline. Henlius has progressed rapidly achieving a number of milestones since its formation in 2010. HCC, hepatocellular carcinoma; NDA, new drug application; nsNSCLC, nonsquamous non-small cell lung cancer; MAA, marketing authorisation application.

Henlius's innovative clinical-phase pipeline features novel inhibitors of VEGFR2, EGFR, PD-1, PD-L1, HER2 and cMET, setting it up to treat a wide range of solid tumors. The earlier-stage pipeline features biologics against targets that include Claudin18.2, CD73, CTLA-4, TIGIT, LAG3, OX40, DR and CD47.

The breadth of Henlius's pipeline positions it to explore immuno-oncology combination therapies globally. Henlius has submitted two combination clinical programs to run global clinical trials, which pair PD-1 inhibitor HLX10 with HLX04 and HLX07, aiming to achieve synergistic effects by targeting VEGF and EGFR, respectively. A combination trial of PD-1 inhibitor HLX10 and biosimilar Avastin HLX04 has already been started. Henlius is equipped to evaluate some of the most promising combinations in the whole cancer field, such as the pairing of a checkpoint inhibitor and an anti-immunosuppressive CD47 molecule.

Henlius is also interested in emerging modalities such as bispecific antibodies, cancer vaccines and oncolytic viruses, positioning itself to stay at the cutting edge of oncology research.

Establishing commercial capabilities

Henlius's global R&D and regulatory registration capabilities equip it to take drugs to market in countries around the world. With three more therapies set to join HLX01 on the Chinese market in the near term, Henlius is building a dedicated marketing, sales and market access team.

The management team at Henlius has identified an independent commercialization strategy as the best way to win market share and create value within China. That strategy leverages the support of Fosun, Henlius's parent company and a major commercial-stage player in the Chinese market.

Henlius is concurrently pursuing a different strategy outside China. In these markets, Henlius partners with global pharmaceutical companies. Henlius has partnered with companies including Accord Healthcare, Biosidus S.A., Cipla and The Jacobson Group to bring its therapeutics to patients across the Americas, Asia and Europe.

In September, Henlius struck another collaboration agreement with a total milestone payment of up to $692 million to illustrate its global strategy for PD-1. The agreement gives PT Kalbe Genexine Biologics (KGBio) the exclusive right to develop and commercialize HLX10 in the Philippines, Indonesia and a total of ten Southeast Asian countries.

The breadth of Henlius's pipeline means there are more partnerships to come. Having established an innovative, fully integrated platform to build a broad pipeline of biologics, Henlius is well equipped to bring a stream of biological products to the market. Now, Henlius is seeking partners to help it get products to patients outside China.

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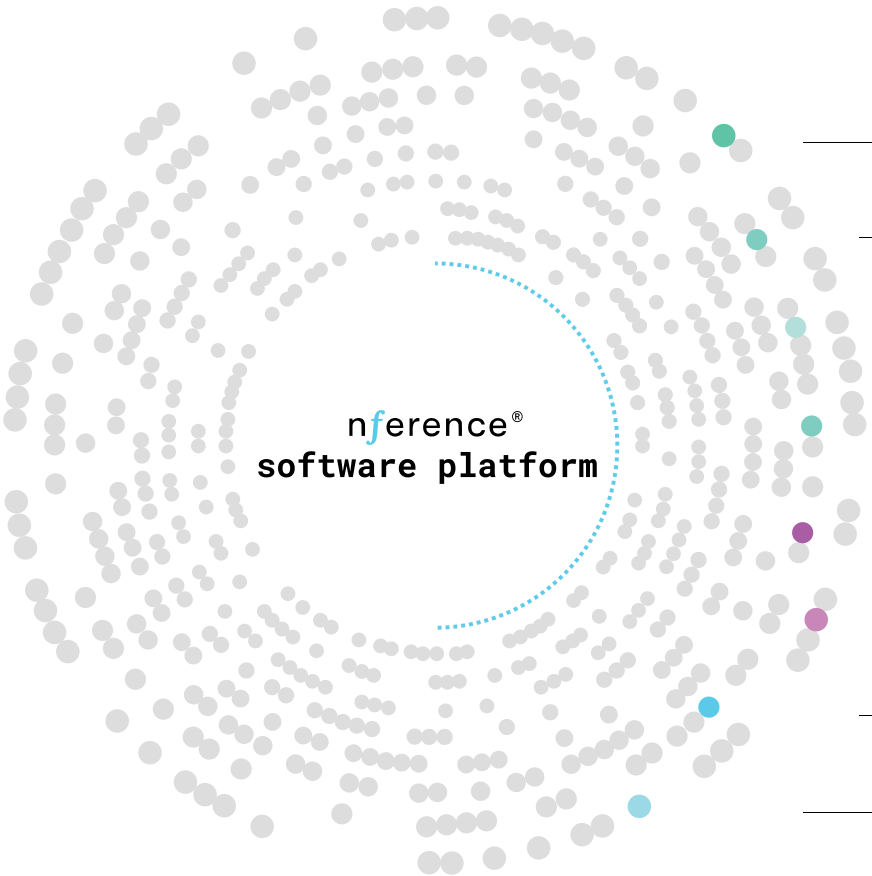
Triangulation Across Data Siloes



data sources

- Electronic Medical Records
- Clinical Trials
- Insurance Claims
- FDA Adverse Events
- Genotypes
- Bulk & Single Cell RNA Seq
- Biomedical Literature
- Others

Powered by Augmented Intelligence, nference synthesizes the world's exponentially growing biomedical knowledge to solve the most urgent healthcare problems of our time. nference uses state-of-the-art machine learning to identify patterns and extract insights from public and proprietary data sets. It is the only holistic platform that integrates data ranging from transcriptomics and imaging to literature and real-world evidence. The nferX® platform is being recognized as the single engine to support drug discovery, clinical research, clinical trial operations and lifecycle management.

Put the world's biomedical knowledge to work.

For more information, visit nference.ai.