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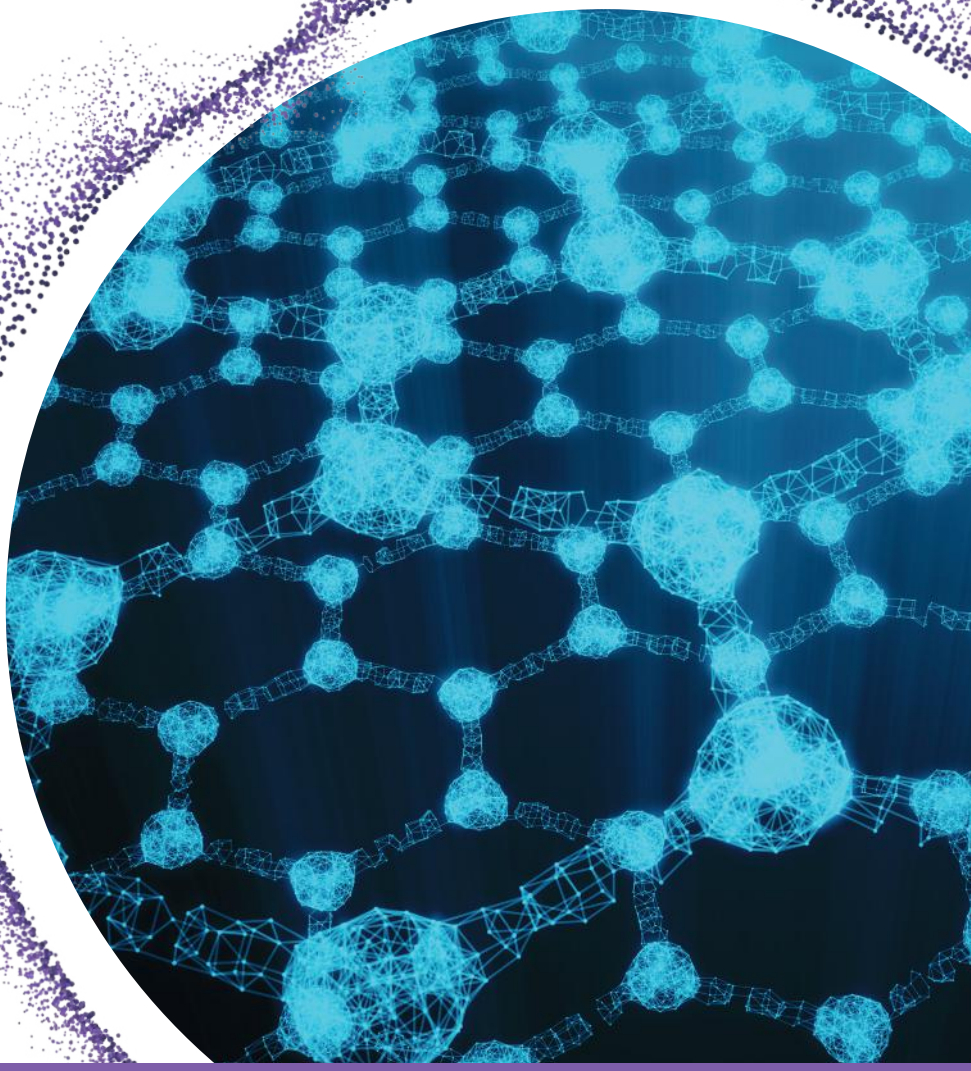
Ebook

Trends In Biotech Innovation



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June 2023

Foreword

Biotechnology innovations have been transforming the way we approach health care and develop new treatments for patients. In the last few decades, this field has witnessed significant advancements, with new technologies emerging at a rapid rate. From gene editing to synthetic biology, biotech innovation has paved the way for new and innovative products and services that are changing the world. Some of the most exciting aspects of biotech innovation is its potential to address some of the most pressing health care challenges we are encountering today across a broad array of rare diseases and hematology/oncology indications.

Biotech companies are in the forefront of developing new therapies and treatments in response to these challenges. Clinical Research Organizations provide these companies with strategic insights, therapeutic expertise, and operational support for developing new drugs and therapies. At the same time, biotech innovations also raise important ethical and social questions that must be addressed. As the field continues to grow and evolve, it is important to ensure that new technologies are developed responsibly and lawfully. This requires open and transparent communication between scientists, policymakers and the public, ensuring biotech innovations are guided by ethical and moral considerations.

The COVID-19 pandemic provided a major impetus in using advanced technologies in improving the effectiveness of vaccines. The studies into the efficacy of mRNA have also led to scientists studying how its superior clinical profile can help in curing other life-threatening diseases. Similarly, improvements in antibody drug conjugate (ADC) technologies and novel cell and gene therapies have led to continued venture capital financing as well as pharma co-development deals funding such innovations and investing in biotech start-ups.

This eBook discusses the future of biotech innovation in health care, the potential of mRNA beyond vaccines, developments in the ADC space, new and upcoming cell and gene therapies and availability of funds for supporting biotechnological innovations that has the potential to impact people's lives across generations. We hope you find these articles informative, useful and inspirational.

Solomon Babani
Senior Vice President & General Partner
ICON

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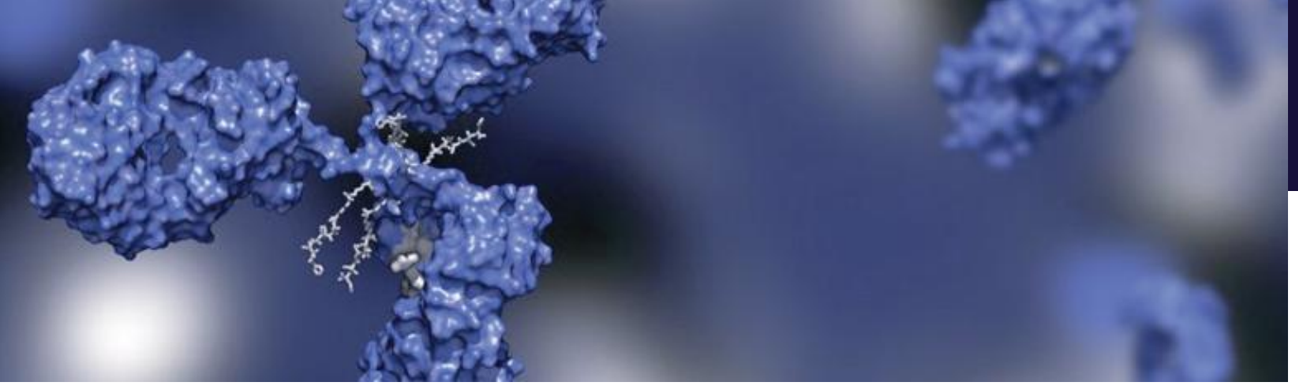


ADCs Coming Of Age: Deals, Targets And Catalysts

Lucie Ellis-Taitt
12 Apr 2023

Executive Summary

The antibody-drug conjugate field is beginning to reach its full potential and big pharma's attention has been caught.

Antibody-drug conjugate (ADC) technology is not new. The first ADC, Pfizer Inc.'s Mylotarg, reached the market two decades ago. The field has undergone slow but transformative enhancements.

"ADC development has historically not been without its setbacks," Datamonitor Healthcare analysts noted in a 2019 report. The concept of delivering a potent cytotoxic payload directly to tumor cells and causing minimum damage to non-tumor cells was viewed as a significant advance towards precision medicine, but it proved difficult to translate into the clinic. Now the field is coming of age, with more products on the market and a busy pipeline channeling new candidates into later stage trials. The number of big-name players in the ADC space is also on the rise.

"The resurgence in ADC development coincides with improvements in ADC platforms, linker technologies and new applications such as combination approaches with immunotherapy and chemotherapy to treat cancer," Datamonitor analysts said.

Next-generation ADCs are also entering the pipeline, even as the first generation of products are still securing global approvals. Mark Enyedy, CEO of ImmunoGen, Inc., describes next generation ADCs as having "innovation to at least one and if not all of the components to the drug."

HOW THEY WORK

ADCs are comprised of a monoclonal antibody (MAb) targeted to antigens on tumor cells conjugated to a cytotoxic payload. The unique feature of ADCs is that they use the MAb component to selectively deliver a highly potent cytotoxic to cancer cells, while at the same time leaving the surrounding normal tissue unaffected. An optimally designed ADC will have:

- a highly selective MAb targeted to a tumor-associated antigen with little or no expression on normal tissue cells;
- a potent cytotoxic agent designed to elicit cell death following internalization in tumor cells; and
- a linker that attaches the MAb to the cytotoxin, which is stable in circulation but releases the cytotoxic payload in target cells.

ADCs typically have less "off-target" action and less toxicity than conventional chemotherapy treatment. "As a result, patients are more likely to be able to tolerate an ADC therapy, potentially remaining on treatment for longer with better therapeutic outcomes and quality of life," highlighted Datamonitor analysts.

There has been less activity surrounding ADC development outside of oncology, though there is potential in other disease areas such as immune disorders and inflammation – where AbbVie Inc. is the leading developer.

ADCS IN THE HEADLINES

In March, Pfizer announced it would pay $43bn in cash to acquire ADC pioneer Seagen Inc. The US big pharma was attracted to Seagen's four approved products – three ADCs and a small-molecule cancer drug – plus candidates in its pipeline. Pfizer expects the purchase will generate $10bn in annual revenue by 2030. (Also see "Pfizer Pays $43bn For Seagen With Goal Of Rapidly, Globally Advancing ADCs" - Scrip, 13 Mar, 2023.)

Edward Tenthoff, a senior research analyst at Piper Sandler & Co, said in a 13 March note that while there was more to the acquisition than Seagen's ADC pipeline and technology, "we do believe this validates the coming of age of ADCs and frees up capital for next-gen ADC and conjugate plays."

Pfizer and Seagen's combined ADC pipelines will place the companies third in the list of top 20 companies active in ADC development (as it currently stands, before any potential consolidation of programs or divestments; the combined portfolios will have 18 ADC programs.)

ImmunoGen's Enyedy said the recent spotlight on the ADCs was positive for companies in the field. His company has seen more interest in recent years from developers looking to partner. "There are a number of companies that have what I call 'naked antibodies' that they think would make good ADCs," Enyedy told In Vivo. "We are regularly approached by companies with these antibodies looking to deploy our linker and payload technology to create an ADC that we can then co-develop."

He highlighted the company's partnership with MacroGenics, Inc. as one example. The two are co-developing IMGC936 as a first-in-class ADAM9-targeting ADC. ADAM9 is a cell surface protein that belongs to the ADAM (a disintegrin and metalloproteinase) family of proteases, which has been implicated in cytokine and growth factor shedding and cell migration. It has been shown that ADAM9 is overexpressed in multiple solid tumor types (eg, non-small cell lung cancer, gastric, pancreatic, triple-negative breast and colorectal) and minimally expressed on normal tissue. IMGC936 is being tested in Phase I studies.

BioNTech SE also announced a significant play into the ADC space in April. The German firm announced exclusive license and collaboration agreements with DualityBio for two antibody-drug conjugate assets to develop and commercialize globally (excluding some Asian markets). DualityBio will receive upfront payments of $170m, as well as potential development, regulatory and commercial milestone payments for both assets, totaling more than $1.5bn. Both products are targeting cancer indications.

TOP 20 PLAYERS

There are a handful of blockbuster ADCs paving the way for more therapies to come to market. Roche Holding AG's Kadcyla (trastuzumab emtansine), Seagen/Takeda Pharmaceutical Co. Ltd.'s Adcetris (brentuximab vedotin) and AstraZeneca PLC and Daiichi Sankyo Co., Ltd.'s Enhertu (trastuzumab deruxtecan) have seen great commercial success. For Enhertu, consensus analyst forecasts predict sales of more than $6bn by 2027.

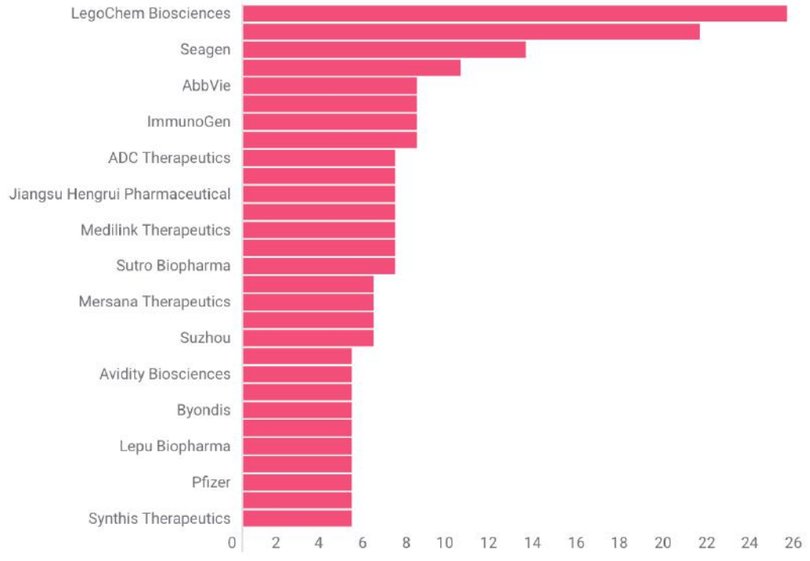
Looking at the ADC pipeline from preclinical development to launched products, LegoChem is the most active company with 25 ADC programs. When narrowing the focus to big pharma only, AbbVie is the most active player with eight programs.

All of the top 10 big pharma companies (according to the most recent Scrip 100 league table) have at least one ADC program in their pipeline.

Top ADC Players In 2023

LegoChem Biosciences is the number one ADC developer with 25 drug candidates in development. However, the majority of its pipeline assets are in the preclinical phase. Its most advanced drug is in Phase II clinical trials. Seagen* has the most advanced portfolio with five launched products and seven clinical-stage candidates.

**Pfizer announced plans to acquire Seagen in March 2023.*

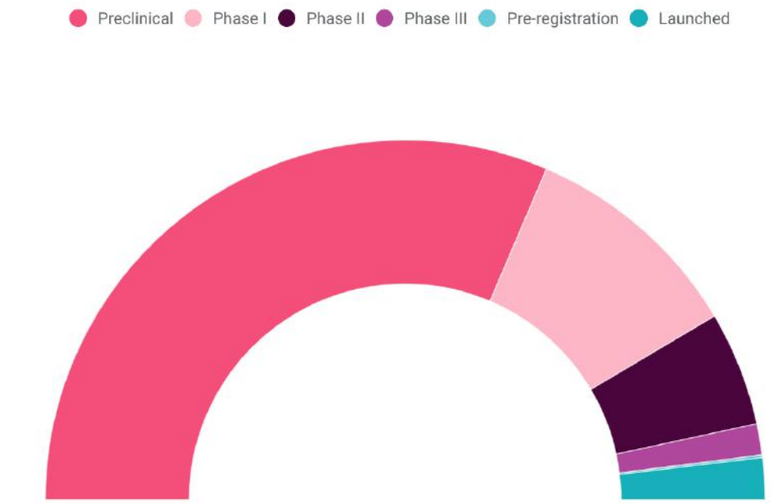


Familiar names have shifted around in the list of leading ADC developers between 2019 and 2023, with some disappearing entirely.

Leading Developers In 2019	# Assets	Leading Developers in 2023	# Assets
ImmunoGen	8	LegoChem Biosciences	25
LegoChem Biosciences	8	Hangzhou DAC Biotech	21
AbbVie	8	Seagen	13
Seattle Genetics (Seagen)	7	Exelixis	10
Daiichi Sankyo	7	AbbVie	8
NBE Therapeutics	6	Daiichi Sankyo	8
Auven Therapeutics	6	ImmunoGen	8
Shanghai Miracogen	6	Zymeworks	8
Pfizer	5	ADC Therapeutics	7
Ambrx	5	Iksuda Therapeutics	7
Bayer	5	Jiangsu Hengrui Pharmaceutical	7
CytomX Therapeutics	5	LaNova Medicines	7
Heidelberg Pharma	4	Medilink Therapeutics	7
Oncomatryx	4	RemeGen	7
Zydus Cadila	4	Sutro Biopharma	7
Roche	4	BiOneCure Therapeutics	6
Sutro Biopharma	4	Mersana Therapeutics	6
Systimmune	4	ProfoundBio	6
BiVictriX Therapeutics	4	Suzhou	6
Rakuten Medical	3	AstraZeneca	5
		Avidity Biosciences	5
		Bio-Thera Solutions	5
		Byondis	5
		Duality Biologics	5
		Lepu Biopharma	5
		Merck & Co	5
		Pfizer	5
		Sichuan Kelun Pharmaceutical	5
		Synthis Therapeutics	5

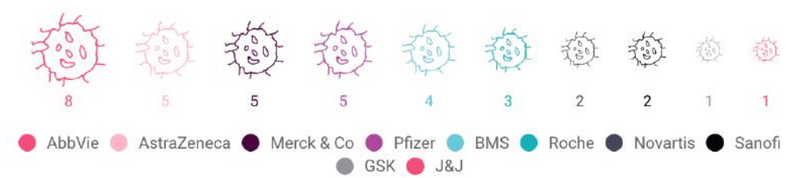
ADC Pipeline By Development Stage

According to data from Pharmaprojects, there are 428 ADC drugs in the pipeline. The majority of assets are in preclinical development.



Big Pharma Players

The top 10 biopharma companies, according to the most recent Scrip 100 ranking, are developing 36 ADC drugs, with the majority targeting cancer indications. AbbVie is developing ADCs against arthritis and Crohn's disease.



Source: Citeline Pharmaprojects. Data correct as of 15 March 2023.

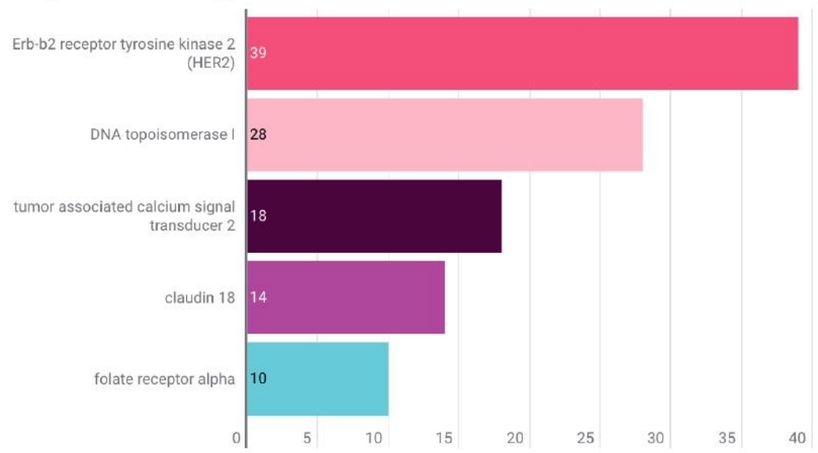
NEW TARGETS

According to data from Pharmaprojects, there are 428 ADC drugs in the pipeline, with the majority of assets in preclinical development. This follows the idea that while a handful of launched products have been successful, industry is focused now on next-generation ADCs with improved efficacy and fewer side effects. HER2 is the most common target for ADC therapies, but other targets are growing in use. Claudin 18 has emerged as a fresh target for ADC developers.

In a 31 May 2022 paper on Claudin 18 as a novel biomarker, published by *BMC (part of Springer Nature)*, the authors noted, "The claudin18.2 (CLDN18.2) protein, an isoform of claudin18, a member of the tight junction protein family, is a highly selective biomarker with limited expression in normal tissues and often abnormal expression during the occurrence and development of various primary malignant tumors, such as gastric cancer/ gastroesophageal junction cancer, breast cancer, colon cancer, liver cancer, head and neck cancer, bronchial cancer and NSCLC."

The authors also said, "Global research and development have demonstrated that CLDN18.2 targeting candidates may become an important alternative for gastric cancer targeted treatment after HER-2-targeted agents."

Top 5 ADC Targets



HER2 is the most common target. This list does not include approximately 178 product candidates in the pipeline for which the target is not specified.

Pharmaprojects, March 2023

BEYOND CANCER

Today, all approved ADC treatments target cancer indications. The three cancer indications with the most approved ADC treatments are: NSCLC (seven approved ADCs), bladder cancer (six) and breast cancer (six). The company with the most approved therapies is Seagen.

Still, the ADC field has some potential beyond the realm of oncology in immunological and musculoskeletal disorders. ADCs have also previously been studied in early trials for cancer pain and myelodysplastic syndrome.

While there are hundreds of pipeline candidates in development for cancer, there are just a handful in other disease areas. Musculoskeletal is leading the way, outside of oncology. There are five drug candidates in clinical development for musculoskeletal indications, all of which are in Phase II. These are being developed by AbbVie, Avidity Biosciences, Inc. and Dyne Therapeutics.

AbbVie also has Phase II programs active in Crohn's disease and rheumatoid arthritis.

PROTECTION AGAINST BIOSIMILARS

Recent discussions, following Pfizer's bid for Seagen, have focused on the question of biosimilar competition for ADCs, and importantly whether these complex drugs are almost immune to biosimilar competition. "The existence of a biosimilar for ADCs is a very complicated issue," Pfizer's CEO Albert Bourla suggested on a company call after the Seagen deal was announced. (Also see "Biosimilar Antibody-Drug Conjugates? Pfizer Isn't Banking On It" - Pink Sheet, 16 Mar, 2023.)

"Large molecules are enjoying by regulation and de facto way larger exclusivity periods, particularly the ADCs, because they are very complex conjugates basically of three biologics in many cases, or two," Bourla pointed out.

Meanwhile, he opined that the regulatory pathway for biosimilars themselves was "very complicated and not well-defined. So, the durability of these assets is way beyond the normal durability of small molecules."

In the days before Pfizer's deal was announced, Seagen's CEO David Epstein had also laid bare the hurdles for biosimilar sponsors, both regulatory and development. "First, the regulatory path has to be determined. It doesn't exist today." He continued, "I don't think, for example, just injecting an ADC and then taking a blood level is going to tell you whether the drugs are the same or not."

Nevertheless, he suggested, "someday, I would imagine there's a biosimilar that can be made." But "it's not any time soon."

ImmunoGen CEO Enyedy agreed that biosimilars of ADC drugs are not in the immediate pipeline: "I certainly would not underestimate the ingenuity of innovators around the world to create biosimilars of antibody-drug conjugates. But among the molecules that one would seek to replicate ADCs are among the more difficult of the class of biologics."

Enyedy added that he expects to see "bio-better" competitors in the future for ADC therapies, rather than straight biosimilar products.

Ameet Mallik, CEO of ADC Therapeutics SA and former head of the biosimilars unit at Sandoz, told In Vivo that at one point people also thought biologics would be immune from copy products. However, he said the process to create an ADC was very complicated. "I would never say never… but the barriers to producing a generic ADC are much higher than what it takes to produce a biosimilar." He added that generic and biosimilar companies would need to develop their current capabilities to be able to produce ADC copy products.

DEAL-MAKING IS ON THE RISE

According to data from Biomedtracker, between January 2018 and March 2023, there have been around 100 licensing deals publicly disclosed that include ADC assets. There were only a handful of licensing agreements identified in 2018, with dealmakers ramping up activity in the early 2020s. Eleven ADC-focused licensing deals were announced in the first three months of 2023 alone.

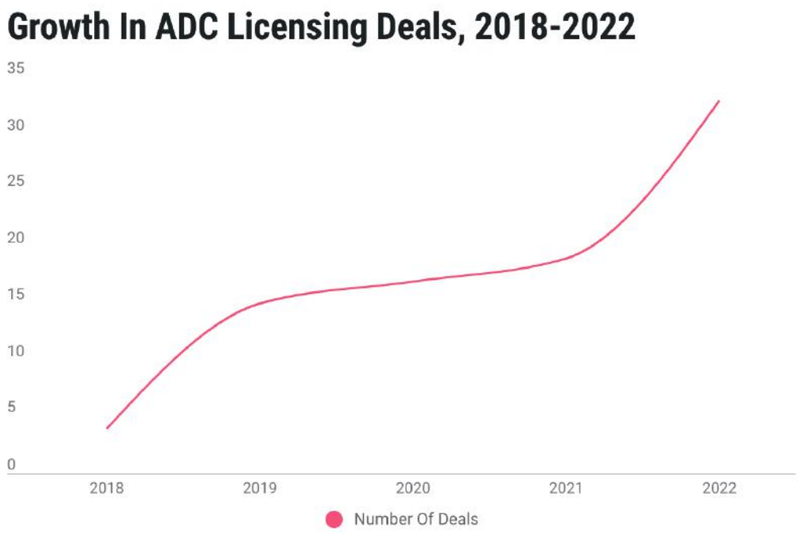
In March this year, ImmunoGen announced a global, multi-target license and option agreement granting Vertex Pharmaceuticals the rights to conduct research using ImmunoGen's ADC technology to discover novel targeted conditioning agents for use with gene editing. Following the research period for each target, Vertex will have the option to obtain a worldwide, exclusive license to research, develop, and commercialize conditioning agents employing ImmunoGen's technology for that target. ImmunoGen will retain full rights to the ADC technology for all targets not covered by the Vertex license. ImmunoGen will receive an upfront payment of $15m and is eligible to receive up to $337m in option exercise fees and development and commercial milestone payments per target.

In January, Amgen signaled its determination to be a major ADC player by signing a huge preclinical deal with Synaffix. Amgen will gain access to Synaffix's ADC technologies for one program with the option to exercise exclusive research and commercial licenses for a further four programs at a later date. Announcing the deal on 5 January, Synaffix did not provide details of any upfront payment, but said a deal signing fee and milestones in the development of four candidates could reach up to $2bn, plus tiered royalties on potential future sales. (Also see "Amgen And Synaffix Alliance Could Be Biggest Preclinical ADC Licensing Deal Yet" - Scrip, 5 Jan, 2023.)

The new deal confirmed that ADCs are a priority for Amgen, coming just days after a very similar licensing agreement with LegoChem, announced on 27 December 2022. This was based on the South Korean company's ConjuAll ADC technology in up to five targets selected by Amgen, and worth up to $1.25bn including upfront, development and commercial milestone payments.

Also signing recent deals, in December 2022, were Merck KGaA, via a pact with Mersana Therapeutics, Inc. worth up to $830m, and Merck & Co. and Kelun-Biotech, in a deal which could hit a maximum value of $9.3bn, based on seven preclinical ADC candidates.

Despite "a flurry of activity," ADC Therapeutics' Mallik expects to see deals become more focused. He said there were two main types of collaborations: companies teaming up to access expertise or products, or deals to license linker, conjugation or toxin technology. "Those are the ones where it will be interesting to see them play out. Getting an ADC right is difficult. There will be a lot of learnings from those deals," Mallik said.



> 11 deals have also been announced between 1 January and 1 March 2023
>
> Biomedtracker

COMMERCIAL EXPECTATIONS

Of the newer ADC market entrants, those launching between 2019 and 2022, Daiichi Sankyo and AstraZeneca's Enhertu (trastuzumab deruxtecan) has been the best performer, with 2022 worldwide sales of $1.3bn, of which $863m came from US sales.

Enhertu is on the rise following a string of regulatory approvals for breast, lung and gastric cancers but new data suggest that the ADC could be an effective treatment for a wide range of other HER2-expressing tumors. AstraZeneca said in March 2023 that high-level results of a mid-stage trial of Enhertu met the prespecified target for objective response rate (ORR) and durable response across multiple HER2-expressing advanced solid tumors in heavily pre-treated patients. The ongoing DESTINY-PanTumor02 Phase II study is evaluating the drug in patients not eligible for curative therapy, including biliary tract, bladder, cervical, endometrial, ovarian, pancreatic and rare cancers. (Also see "AstraZeneca/Daiichi Sankyo Line Up More Enhertu Indications" - Scrip, 6 Mar, 2023.)

No specific results from the 268-patient study were revealed but AstraZeneca said the data would be presented at an upcoming medical meeting. The safety profile in DESTINY-PanTumor02 was consistent with that seen in other trials of Enhertu with no new signals identified. Enhertu has become a major pillar of AstraZeneca's oncology franchise since the firm agreed to pay $1.35bn upfront and up to $6.90bn in total for the ADC.

Enhertu already enjoys blockbuster status. Analysts predict it could hit nearly $6bn in peak annual sales, especially if a label expansion is granted for earlier-stage breast cancer; AstraZeneca and Daiichi Sankyo are scheduled to report data from the Phase II DESTINY-Breast06 trial in second-line HER2-low breast cancer in the second half of 2023.

ImmunoGen's Elahere, which has only been on the market for one full quarter, is expected to report better-than-expected sales. "We will have revenue for the first quarter at the end of April and the launch is exceeding our expectations," Enyedy told In Vivo.

Elahere is ImmunoGen's first independently owned drug, although the company's ADC technology was used for the early development of Roche's Kadcyla and Sanofi's Sarclisa (isatuximab).

Enyedy, who previously held leadership roles at Genzyme and Shire before becoming CEO of ImmunoGen, said the volume of testing for patients eligible for treatment with Elahere was above the company's expectations for the first quarter of 2023. He noted that 1,500 patients had been tested in the first six weeks after launch and the volume of testing had "only accelerated since the beginning of the year."

The company had also been surprised by the "breadth and depth of adoption" of Elahere quickly after its launch. "Our initial view of this product was that it was likely to see early adoption, from a commercial perspective, in the large academic centers where the clinical studies have been run," Enyedy said. "In addition, what we're seeing is broad community use: 75% of our orders have come from community physicians." (Also see "ImmunoGen's First ADC For Ovarian Cancer To Exceed Sales Expectations" - Scrip, 3 Apr, 2023.)

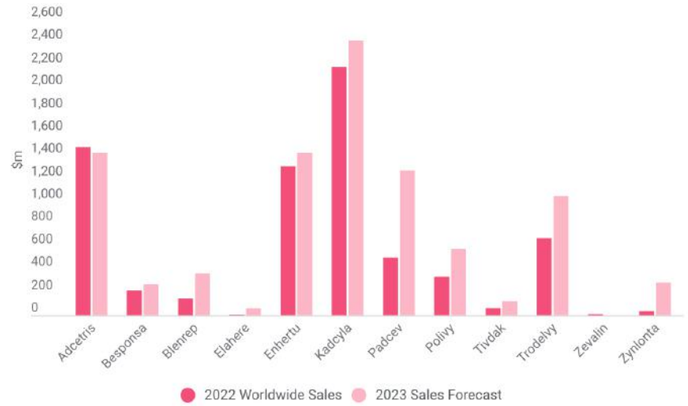
As of March 2023, Biomedtracker analysts were forecasting total 2023 worldwide sales of $62m for Elahere.

ADC Therapeutics has a busy pipeline of ADC candidates, with several critical clinical trial readouts coming up in 2024. This pipeline, as well as the company's one approved ADC Zynlonta (loncastuximab tesirine), were what attracted Mallik to the CEO position. He joined the company in 2022, having previously held leadership roles in Novartis and been CEO of Rafael Holdings, a cancer and immune metabolism therapeutics company.

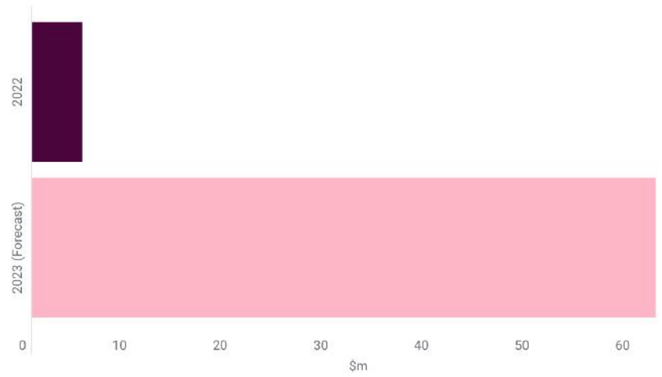
Mallik highlighted that not many companies had been able to bring ADCs to market, so far. ADC Therapeutics' approved treatment "validated a lot of capabilities across the value chain," Mallik said. "Having a commercial product, also with the potential for expanding earlier lines of treatment, you could see a successful a path towards profitability, which is a rare thing in biotech."

Zynlonta, which is approved for diffuse large B-cell lymphoma, had worldwide sales of $75m in 2022.

Kadcyla Tops The Table As Biggest ADC Earner



Spotlight On Elahere: 2023 Sales Consensus



All FDA Approved ADC Therapies

Drug	Lead Company	Indication/s	First Approval
Enhertu	Daiichi Sankyo	NSCLC; gastric cancer; breast cancer	2019
Zynlonta	ADC Therapeutics	DLBCL	2021
Blenrep	GlaxoSmithKline	Multiple myeloma	2020
Tivdak	Seagen	Cervical cancer	2021
Trodelvy	Gilead Sciences	Bladder cancer; breast cancer	2020
Elahere	ImmunoGen	Ovarian cancer	2022
Polivy	Roche	DLBCL	2019
Padcev	Astellas	Bladder cancer	2019
Besponsa	Pfizer	ALL	2017
Kadcyla	Roche	Breast cancer	2013
Adcetris	Seagen	NHL; Hodgkin's lymphoma	2011
Mylotarg	Pfizer	AML	2017 (reinstated)
Zevalin	Aurobindo Pharma	NHL, follicular lymphoma	2002

Source: Biomedtracker
Note: No sales data available for Mylotarg.

2023 ADC CATALYSTS

In early April 2023, Merck & Co., Inc.'s PD-1 inhibitor Keytruda won US approval for use in combination with Seagen Inc. 's ADC Padcev for the treatment of first-line urothelial carcinoma in an industry first. (Also see "Merck's Keytruda And Seagen's Padcev Become First PD-1/ADC Combo To Win US Approval" - Scrip, 4 Apr, 2023.)

The FDA approved Keytruda (pembrolizumab) with the nectin-4-directed antibody and microtubule inhibitor ADC Padcev (enfortumab vedotin) for first-line locally advanced or metastatic urothelial carcinoma patients ineligible for cisplatin-based therapy under an accelerated pathway several weeks in advance of the 21 April Prescription Drug User Fee Act date.

This marks the first time an anti-PD-1 has been approved in combination with an antibody-drug conjugate in the US, but continued approval will be contingent upon data from the ongoing confirmatory KEYNOTE-A39 trial.

Looking ahead through the year, there a number of regulatory decisions for ADC therapies expected in the US and Europe, as well as pivotal clinical trial readouts over the next one to two years.

In the US, Byondis has a PDUFA action date of 12 May 2023 for trastuzumab duocarmazine (SYD985) in patients with HER2-positive unresectable locally advanced or metastatic breast cancer. SYD985 has demonstrated an increase in PFS and OS when compared to physician's choice of treatment in heavily pretreated HER2-positive metastatic breast cancer patients. The FDA granted fast track status to the ADC treatment after it demonstrated promising early efficacy results in a Phase I study in HER2+ metastatic breast cancer patients who had progressed during or after at least two HER2-targeting treatment regimens for locally advanced or metastatic disease.

While Phase III results have been positive, and will likely result in approval in this setting, SYD985's commercial potential is limited by the increasingly crowded third-line market and Synthon's limited oncology marketing experience and resources in comparison to competitors, particularly Daiichi Sankyo and AstraZeneca. SYD985 is also in development for uterine cancer (Phase II) and solid tumors (Phase I). (Also see "Byondis Seeks Partner For Lead ADC To Enter Crowded Breast Cancer Market" - Scrip, 9 Jun, 2021.)

European marketing authorization for SYD985 for this indication is also expected between April 2023 and October 2023.

Further out, Mersana Therapeutics is preparing for US accelerated approval of upifitamab rilsodotin for ovarian cancer in 2024.

OTHER IMPORTANT UPCOMING ADC PIPELINE EVENTS

Elahere MIRASOL Data

Top-line data from the confirmatory Phase III MIRASOL study for ImmunoGen's Elahere in ovarian cancer are expected in the first half of 2023. Elahere received accelerated approval from the FDA on 14 November 2022 for the treatment of folate receptor alpha (FRα)-positive, platinum-resistant epithelial ovarian, fallopian tube or primary peritoneal cancer in patients following three prior systemic treatment regimens and regardless of prior treatment with Avastin.

The accelerated approval, which came nearly two weeks ahead of the action date, was based on clinical trial data showing improvement in objective response rate (ORR) and duration of response (DOR) from the pivotal SORAYA trial.

The FDA's approval of Elahere under the accelerated approval pathway was likely smoothed by the fully enrolled MIRASOL clinical trial. (Also see "Keeping Track: Early Thanks Given By ImmunoGen, Provention Bio; More PD-1/L1 Combo Approvals" - Pink Sheet, 18 Nov, 2022.)

The MIRASOL trial will form the basis for a regulatory submission for Elahere in Europe, along with a contemporaneous submission to the MHRA for the UK. The company also has a collaboration in China with Huadong Medicine, where the drug is expected see a regulatory submission later in 2023 – targeting approval in 2024.

TROPION-LUNG01 Study Of Datopotamab Deruxtecan
Daiichi Sankyo and AstraZeneca will release topline results from the Phase III TROPION-LUNG01 clinical trial in early 2023 for datopotamab deruxtecan in NSCLC with or without actionable genomic alterations.

Datopotamab, which targets TROP2, is also in late-stage development for use in breast cancer (both triple-negative and HR-positive/HER2-negative). TROP2 (trophoblast cell-surface antigen 2) is a transmembrane glycoprotein that is widely expressed in several types of solid tumors.

Tusamitamab Ravtansine In CARMEN-LC03
Sanofi's tusamitamab ravtansine (SAR408701) is the most advanced ADC to target CEACAM5. CEACAM5, or anti-carcinoembryonic antigen-related cell adhesion molecule 5, is a member of the CEA family of proteins which plays a key role in cell migration, cell invasion and cell adhesion, and is overexpressed by a variety of cancer cell types. Topline data from the Phase III CARMEN-LC03 study in CEACAM5-positive second- and third-line NSCLC patients are due in the first half of 2023. It has two primary endpoints: improvement of progression-free survival compared with docetaxel up to 15 months and improvement in overall survival compared with docetaxel up to two years.

DREAMM-7 Blenrep Trial
GlaxoSmithKline and Seagen are expected to produce data for Blenrep from the Phase III DREAMM-7 in 2023. GSK's blockbuster hopes for the BCMA-targeting Blenrep (belantamab mafodotin) took a hit when the product was taken off the US market late last year at the FDA's request after the drug failed to show significant PFS benefits in the Phase III DREAMM-3 confirmatory study. (Also see "Blenrep US Withdrawal Is A Big Blow To GSK's Blockbuster Hopes" - Scrip, 22 Nov, 2022.)

Blenrep was conditionally approved in the US in August 2020 for relapsed/refractory multiple myeloma, and later that same month by the European Medicines Agency, based on response rates in the DREAMM-2 study, for patients who have received at least four prior therapies including an anti-CD38 monoclonal antibody, a proteasome inhibitor and an immunomodulatory agent. The drug was the first BCMA-targeting agent to gain approval in myeloma, but eye toxicity concerns had already contributed to a modest launch trajectory – it only reached £36m ($42.8m) in revenues in the third quarter of 2022.

The product's future now rests largely on data from DREAMM-7 and DREAMM-8, both due in 2023, along with efficacy ocular, toxicity will be a key consideration.

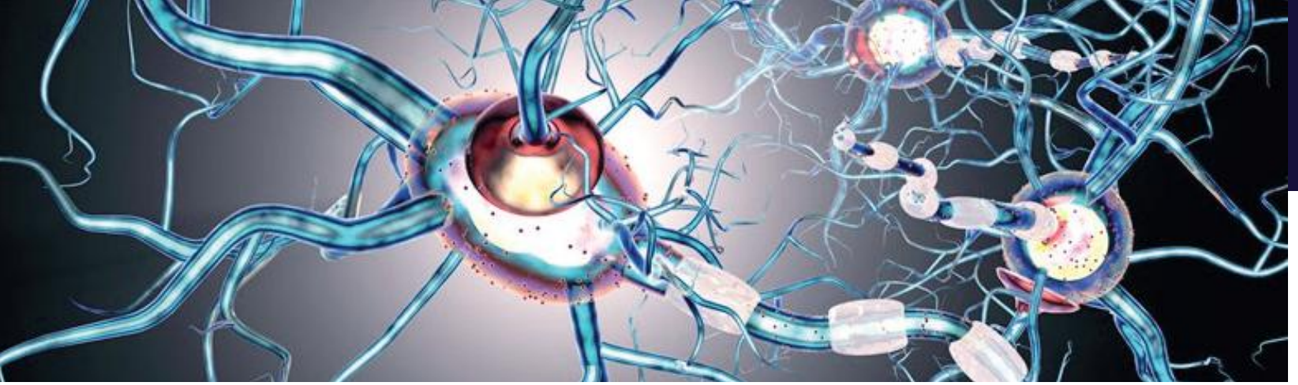
TAKING NEXT-GEN TO THE NEXT LEVEL

The ADC field will not be short on headlines over the coming few years and the R&D space is very much in vogue. Despite products coming to market and late-stage clinical trials reading out critical data insights though, there is still more to uncover in ADC development.

ADC Therapeutics' Mallik said: "As an industry, we've been working with a small set of payloads up to this point and the number of potential payloads, both toxin and not toxin, such as immunostimulants, is just expanding."

Mallik added that he saw a world of potential for the future of ADCs. For example, the future could include bi-specific ADCs or ADCs with dual payloads.

The CEO wants to see continued improvement in ADC technology to expand the therapeutic index and reduce systemic toxicity when treating cancer.



Rare Opening In Tough Times: New Biotechs Rekindle CNS Development In China

But Regulatory Barriers Remain

Brian Yang
14 Apr 2023

Executive Summary

A slew of high-level executives has established biotech startups in China with a single focus on CNS conditions. Emerging collaboration and funding flow highlights a heating up market, but insiders tell *Scrip* that choppy waters and an uncertain future may be looming.

After leading a Nasdaq-listed Chinese biotech, I-Mab Biopharma Co., Ltd, as CEO for years, Joan Shen has started and is CEO of her own new bioventure, NeuShen Therapeutics, which is focusing on central nervous system conditions.

The first target disorder for the Shanghai- and Lexington-based startup is amyotrophic lateral sclerosis (ALS), a rare and rapid progressive neurodegenerative condition. The Shanghai firm has already closed an initial pre-A round funding of $20m from a group of Chinese investors and opened an R&D center in the US, and is collaborating with the University of Massachusetts.

The academic partnership will focus on an adeno-associated virus-based gene therapy for the condition and the new company also intends to develop small molecule drugs for ALS.

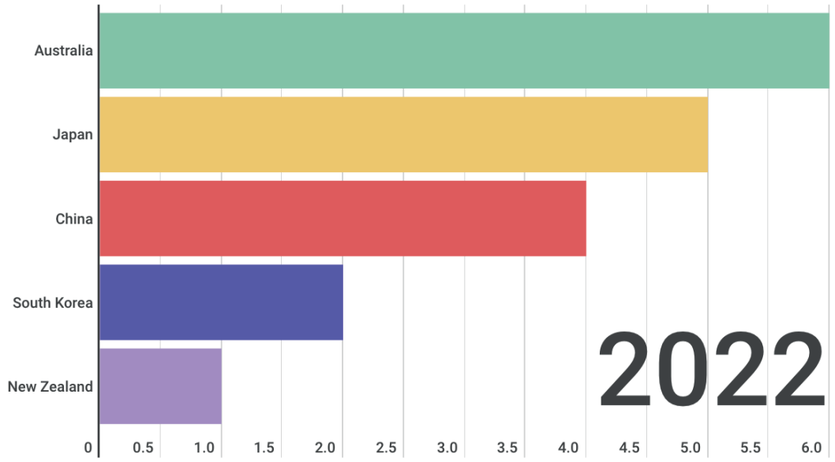
Shen is not alone in taking the plunge with a new venture, however, and is just one of many high-level returnee pharma executives who have started their own biotechs in China over the past few years and concentrating on rare CNS conditions, although the majority of such operations are devoted to cancer.

At least 22 companies have flocked into CNS drug development in China, among them NeuExcell Therapeutics Inc. whose chairman is former Novartis AG China president Yin Xudong.

Another, 4B Biotech, was founded jointly by former GSK plc China R&D vice-president Guan Xiaoming and Tsinghua University professor Lu Bai.

APAC Clinical Trials For ALS Drug Development 2013-22 (data from TrialTrove)

APAC Clinical Trials For ALS Drug Development 2013-22 (data from TrialTrove)



Click here for the dynamic infographic.

APAC AS A SITE FOR CNS R&D

Given the emerging new modalities of mRNA and gene therapy, rare CNS conditions such as ALS are moving into the spotlight, not only in China but in Asia Pacific as a whole.

Seizing the opportunity to bypass conventional small molecules, Chinese biotechs are also betting on partnerships with leading researchers in the US to accelerate development. Professor Guo Guangping, a leading expert on AAV families for use in gene replacement therapies, is sought after not only by CNS developers but also other firms working on rare diseases in China.

Elsewhere in APAC, Japanese drug makers are leading regional CNS development, with Eisai Co., Ltd. having obtained multiple approvals in the field, including in the US for Alzheimer's disease drug Leqembi (lecanemab). Otsuka Pharmaceutical Co. Ltd., meanwhile, is a leader in schizophrenia and psychiatric disorders, with its blockbuster Abilify (aripiprazole) franchise.

In South Korea, local companies are active in gene and cell therapy, including ViroMed Biopharma, which has started trials for donaperminogene seltoplasmid, a gene therapy for ALS.

Rare Opening In Tough Times: New Biotechs Rekindle CNS Development In China

Around the APAC region, 116 trials have taken place for ALS over the past decade, led by Japan and followed by China, which is quickly emerging as a center for global CNS research (*see dynamic infographic above*). Data from Citeline's Trialtrove show that a total of 22 trials have taken place in the country for the condition over the 2013-22 period, run by a variety of multinationals and domestic firms.

SPEED IS KING

Amid the blossoming CNS research in China, there is also anxiety around additional and sustained financial support, which is looking increasingly uncertain given the global biotech funding challenges. Bioventures taking assets into the clinical stage face skyrocketing costs and a need for ongoing funding and must not rest on their laurels to compete, especially given long development times and uncertain regulatory approval, executives told Scrip.

The US approval of Amylyx Pharmaceuticals, Inc. Relyvrio (sodium phenylbutyrate/ taurursodiol) for ALS last October has provided other global impetus to the sector, although this was not without some controversy given a strong lobbying presence for the disease in Washington.

So far no gene therapy has gained approval for the disease and APAC is also lagging in venture capital funding for CNS, which makes sustained support for the slew of new startups uncertain.

In China, aside from traditional Chinese medicines, several ALS drugs including edaravone, developed by Japan's Mitsubishi Tanabe Pharma Corporation and domestically by Nanjing Yoko BioMedic, have been approved. However, even local patients are still looking for more effective treatments and a gene therapy with the promise of curing the condition has many excited about the possibility.

So far, Chinese biotechs seems to be betting on quickly entering into the preclinical/clinical stage to accumulate data and executives at the recently founded companies say the winning recipe will be to rapidly build up the pipeline.

A recent multimillion dollar deal between BioNTech SE and Durality Bio in Suzhou has many believing that as long as there is true innovation, there will be potential buyers or licensees. Executives are hoping a good pipeline will help secure funds, although the overall capital crunch may work against them.

Even some more established gene therapy developers such as Belief Biomed Inc., which has a clinical-stage therapy for hemophilia A, are scrabbling for cash.

REGULATORY BARRIERS

Apart from funding and R&D anxiety, the new set of biotech founders see remaining regulatory hurdles for gene and cell therapy developers.

Given that they are founded mainly by Chinese American returnees, the companies, - according to current Chinese regulations - may face challenges to enter gene-related development due to strict rules around the field. Under China's opaque human genetic resources management regulations, foreign companies must register, file and get approvals prior to collecting, storing and using human samples.

In a tit-for-tat tactic to respond to Washington's restrictions over the export of key technologies to China, Beijing is also banning gene- and gene editing-related technology exports, which could further complicate the prospects for some developers.

But the flip side is that recent regulations to encourage rare disease drug development in China, issued by the Center for Drug Evaluation, give pediatric and rare condition treatments a specific timeframe in which developer can be expected to have communications with regulators.

mRNA: The Future Beyond COVID Vaccines

Wen Xie, BCG, Alumna
John Wong, BCG, Managing Director and Senior Partner
Sven Fraterman, BCG, Managing Director and Partner
13 Mar 2023

Executive Summary

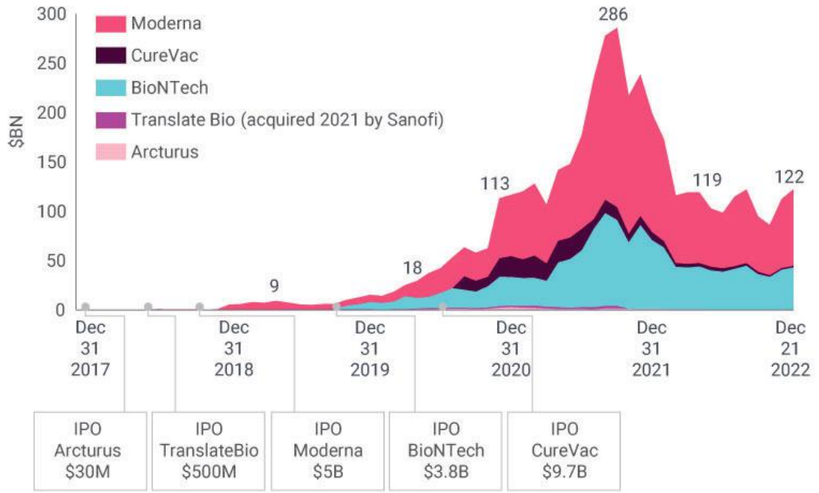
Messenger RNA (mRNA) prophylactic vaccines have made major breakthroughs in 2020 and 2021 with both the Pfizer/ BioNTech and Moderna COVID-19 vaccines gaining approval in more than 150 countries. These mRNA COVID vaccines have been developed much faster and with superior clinical profiles when compared to other more conventional modalities.

The success of mRNA vaccines against COVID-19 has driven a new wave of investment that could accelerate the exploration of mRNA application in other spaces. The market cap for mRNA publicly listed companies once reached ~$280bn in Sep 2021. Since 2008, the mRNA pipeline has grown significantly, almost tripling over the past two years.

This is just the start. Current mRNA therapies in development can be classified into three major applications based on their underlying mechanisms of action:
1. Prophylactic vaccines
2. Therapeutic vaccines
3. Therapeutic treatments

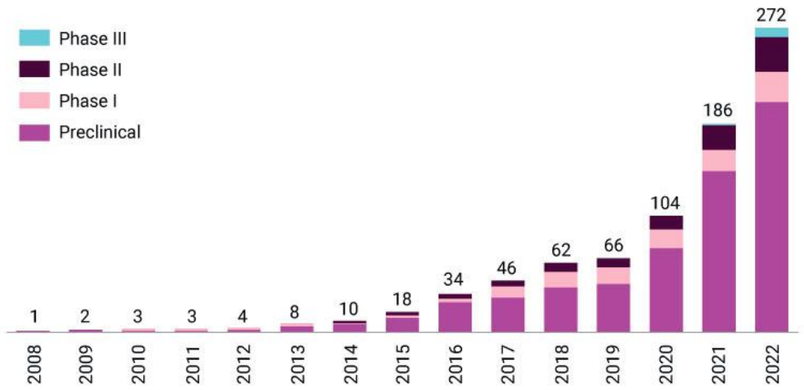
Beyond COVID vaccines, R&D efforts have already shown the potential of mRNA therapy in novel applications including use as therapeutic vaccines and, to a lesser extent, therapeutic treatments. In this article, we focus on the technological promise and market perspective of mRNA, and how biopharma players need to think through their strategies in the mRNA space.

Exhibit 1: Market Cap Of Publicly Listed mRNA Companies[1]



1. not including partners' market cap (e.g., Pfizer)
Source: Company press releases, Citeline Pharmaprojects, Capital IQ, BCG analysis

Exhibit 2: Number Of mRNA Preclinical And Clinical Pipelines Over Years



PROPHYLACTIC VACCINE: INITIAL PROOF OF CONCEPT

mRNA was first discovered in 1961 by Sydney Brenner, but its earliest documented use in disease treatment was in the 1990s by GF Jirikowski. The concept was simple: inject mRNA strands encoding a desired protein into the human body to allow in vivo translation. In the meantime, scientists made significant progress in addressing key challenges to translate science into clinical applications, including nucleoside modification to improve the half-life of the mRNA, and adopt lipid nanoparticles (LNP) or lipoplex for delivery.

Prophylactic vaccine became the first application where mRNA demonstrated its value over traditional modalities in terms of fast development speed, higher immunogenicity and potentially broader variant coverage. These superiorities have been demonstrated in the case of COVID-19 vaccine development, which has served as a great "proof of concept" for mRNA.

However, the superiority in efficacy is not guaranteed for all diseases, with the mRNA vaccine only delivering so far on par, if not inferior, immunogenicity (in influenza, for example). There is also evidence showing initial signs that mRNA could offer a new path to some severe infectious diseases without an effective vaccine such as HIV and Malaria. However, it is still early days for the clinical data.

Biopharma could utilize prophylactic vaccine as a starting point to test their mRNA platform, however we see multiple challenges, particularly on less severe diseases with mature alternatives:

- Clinical trial conduct: finding patients while there is already a commercial option, e.g. in case of Monkey pox
- Regulatory: proving superiority with an active control arm
- Commercialization: crowded market to launch new products e.g. in case of HPV and influenza

THERAPEUTIC VACCINE: PERSONALIZED SOLUTION UNIQUE TO MRNA

Despite the success of immuno-oncology PD-(L)1 class of drugs, there are still high unmet medical needs due to lack of efficacy in certain cancers with aberrant genes, and relapses on IO therapies. The mechanism of action for therapeutic vaccines is like prophylactic vaccine, but instead of activating self-immune cells towards viruses or bacteria, it is against cancer cells. However, while the "external bugs" have quite similar antigens, the cancer cells vary much more across patients, which calls for the vaccine to be more "personalized".

The nature of mRNA drugs makes it "programmable" to target almost any type of mutations, including some difficult-to-target ones by small molecule drugs (e.g. KRAS G12C, G12D, G12V, G13D). And mRNA can target multiple mutations in the same shot. This allows mRNA to be uniquely positioned for personalized cancer vaccines (PCV) (see Table 1).

Early clinical results have shown initial efficacy of such a PCV concept. For example, Phase IIb results of Moderna and Merck's jointly develop PCV mRNA-4157 combined with Keytruda in Stage III/IV melanoma patients (after complete resection) showed clinically meaningful improvements of recurrence free survival compared to Keytruda alone. While interim data of Phase I in checkpoint inhibitor naive HPV head and neck carcinoma also showed ORR of 50% and mPFS of 9.8 months for PCV combined with Keytruda, which compared favorably to the published ORR and mPFS of 14.6% and 2.0 months for Keytruda monotherapy.

However, we see several major challenges faced by mRNA in cancer therapeutic vaccine before it reaches inflection point: limited efficacy as single-drug, or in late-line cancer patients; and complex process to obtain patients' personalized blueprint and manufacture at reasonable cost.

Table 1: Example pipeline items across two different classes of mRNA therapeutic vaccines

MOA	Drug	Company	Indication	Highest Phase	NCT Number
Single antigen					
Onco-antigen E6/E7	BNT-113	BioNTech	HPV16, head and neck cancer	Phase II	NCT04534205
KRAS	mRNA-5671	Moderna/Merck	KRAS-mutated lung cancer	Phase I	NCT03948763
Multiple antigen					
Multiple neoantigens	mRNA-4157	Moderna/Merck	Solid tumors (Ph I), malignant melanoma	Phase II	NCT03897881 (Ph II in Melanoma NCT03313778 (Ph I in Solid
Melanoma antigens	BNT-111	BioNTech	Advanced melanoma (adjuvant and metastatic)	Phase II	NCT04526899
Individualized vaccines against cancer mutanome	BNT-122 (RO7198457)	BioNTech/Roche	Colorectal Cancer Stage II and III, Melanoma with CPI	Phase II	NCT04486378 (Ph II in colorectal cancer), NCT03815058 (Ph II in melanoma)
PD-1, TLR7	BNT-112	BioNTech/Roche	Prostate Cancer	Phase I/II	NCT04382898
Individualized vaccines against cancer mutanome	BNT-114 (IVAC_W_bre1_uID)	BioNTech	TNBC	Phase I	NCT02316457

This calls for a deliberate strategy for biopharma to pursue mRNA personalized cancer vaccine (PCV) which includes:

1. An optimized clinical strategy. To demonstrate clinical superiority to standard of care (SoC), biopharma needs to think through the best clinical path, including indication selection, patient lines and combo strategy. In general, despite showing efficacy in late line patients that run out of treatment options, we see evidence that increasingly suggests that is not the cohort most suitable for mRNA vaccine, as effectively activating immune cells depends on the competency of the patient's own immune system. In addition, cancer patients' immune systems are generally suppressed, and co-administering an immune modulator (e.g. PD-1) could potentially boost efficacy.

The market size for mRNA targeting early line/ low cancer burden patients in combo with I/O is significant. PD-1 has created a $50bn immuno-oncology market, which will excite large biopharma if they add another tangible drug to their I/O portfolios to share or even grow the pie. But on the other hand, early line patients and combinations means longer clinical trials, and riskier head-to-head comparisons (with PD-(L)1).

2. A right go-to-market model, including:

- Effective companion diagnostic for tumor antigen profiling
- Personalized manufacturing
- IT solution for data collection, analysis and storage
- Pricing model

The turnaround date for tumor cell sequencing to generating an effective mRNA vaccine is typically ranging from a couple of days up to eight weeks. And due to the personalized manufacturing process, the cost could be enormous (around $100,000 per patient).

A partnership with genome sequencing companies could potentially enable a more "at-scale" process to both speed up the process and lower the cost. In addition, the data collected could also enable an evolving developmental strategy to further improve the clinical profile. Given these challenges, we anticipate that mRNA therapeutic vaccine pioneers are likely to go through a trial-and-error clinical and go-to-market approach in the next few years. Once the hurdles are overcome, the first mover will establish the market, then likely a wave of mRNA drug developers will either partner with first movers to add value and strengthen their leadership roles, or develop their own pipelines as fast-follower or "me-betters".

THERAPEUTIC TREATMENT: OPPORTUNISTIC FOCUS FOR MRNA

The application of mRNA in therapeutics opens a new set of opportunities in disease areas for mRNA other than oncology and infectious diseases, and also provides alternative solutions to modalities.

In therapeutic treatments, the mRNA encodes the missing / defective protein or protein machinery of interest for therapeutic purposes or immune cell engagement, which theoretically could enable mRNA to target a wide range of diseases and strongly compete with or even substitute other modalities e.g. mAbs, gene therapies, multi-specific antibodies. However, mRNA has inherent limitations that makes it particularly difficult to be successful in all therapeutic classes. We remain prudent to what mRNA could address in the broader disease space.

Therapeutic treatments can be further categorized into three classes: stimulators, inhibitors, and machineries (e.g., gene editing) (see Table 2).

mRNA as a therapeutic treatment has unique advantages in making difficult-to-make proteins inside the body, and only having a transient efficacy to avoid potential side effects due to sustained activation from use of machineries (e.g. gene editing). However, mRNA faces several challenges before it could become a successful therapeutic modality:

- Lack of organ selectivity: currently primarily uptake by liver due to lipid-based delivery systems, selective uptake by other diseased organs or tissue remains uncertain. This problem could potentially be by-passed by local delivery (i.e., intra-tumoral injections)
- Low sustainability and bioavailability: Unprotected mRNA half-life is 6-12 hours, and its low bioavailability also limits the amount of effective therapeutic proteins produced to generate a sustained therapeutic effect
- Immunogenicity/toxicity: It would be challenging to infuse the human body with high doses of mRNA as it will cause toxicities to the liver due to delivery vehicles, and immunogenicity issues.

As a result, we believe it will be challenging to use current mRNA technology to target inhibitory pathways before solving the above issues. Typically, inhibitors act as brakes to biological processes, which require a significant sustained amount of inhibitory substance to be delivered to get any meaningful clinical efficacy. Compared, siRNA, ASOs and miRNA provide better solutions to inhibitory therapeutics. Some novel approaches of mRNA technology such as circular RNA (e.g., Laronde, ORNA) might be able to provide a path to tackle the above challenges and thus expand the therapeutic possibilities of mRNA.

Table 2: Example Pipeline Items Across Three Different Classes Of mRNA Therapeutic Treatments

MOA	Drug	Company	Indication	Current Phase	
Stimulator / accelerator: adding a ligand / receptor to stimulate certain cell functions or to supplement for dysfunctional part					
VEGF	mRNA-8601 (AZD8601)	Moderna/AZ	Myocardial ischemia	Phase II	NCT03370887
OTC	LUNAR-OTC (ARCT-810)	Arcturus	Ornithine Transcarbamylase Deficiency	Phase II	NCT04442347 (in patients NCT04416126 (in health subjects) NCT05526066 (in patients)
TLR7/8/RIG-1	CV8102	CureVac	Cutaneous melanoma, adenoidcystic carcinoma, squamous cell cancer of skin, head and neck	Phase I	NCT03291002 (Ph I in cMEL, cSCC, hnSCC, and ACC), NCT02238756 (Ph I in rabies), NCT03203005 (Ph I/II in Hepatocellular Carcinoma)
IL-12, IL-15, GM-CSF, IFN	BNT-131 (SAR-441000)	BioNTech	Solid Tumors	Phase I	NCT03871348
IL-12	MEDI-1191	Moderna/AZ	HNSCC, MEL, CRC, NSCLC, GC etc.	Phase I	NCT03946800
OX40L, IL-23, IL-36 gamma	mRNA-2752	Moderna	Lymphoma; Solid tumours	Phase I	NCT02872025 (DCIS) NCT03739931 (Advanced Malignancies)
PD-L1	mRNA-6981	Moderna	Autoimmune hepatitis	Preclinical	NA
Inhibitor / brake: adding molecule to stop overly expressed function / pathway					
NA					
Machineries / steering wheel: replace malfunctioning protein with well-behaved substitute					
CRISPR cas-9	NA	CureVac	Lung respiratory diseases	Preclinical	NA

There are some opportunities for mRNA therapeutics as “stimulators” via amplification effect, where lower concentrations of ligands could produce a therapeutic effect. In general, IO stimulators have been traditionally under-developed as stimulatory antibodies (“agonists”) are more difficult to generate compared to inhibitory antibodies (antagonists). As such, mRNA therapy is uniquely positioned to target stimulatory IO pathways compared to other modalities, for example, OX40, IL-12 (MedImmune’s MEDI1191, for example). However, broad application of mRNA in stimulatory IO is circumvented by limited understanding of immune activation target pathways. In other stimulatory settings, such as supplementing defective proteins in rare diseases (e.g., CFTR), or delivering a protein with therapeutic effect (e.g. VEGF in myocardial infarction), mRNA may also be able to provide clinical benefits. Yet targeted organ delivery and sustainability could still make it challenging (the failure of TranslateBio’s MRT5005 in a Phase II trial for cystic fibrosis, for example).

As such, mRNA therapeutics overall should be assumed significant risks. Companies thinking of betting on mRNA therapeutics should scrutinize the diseases etiology and deliberately pick the ones that are suitable for mRNA. We also envision a few catalysts to mRNA therapeutics:

- Scientific and translational research progress of I/O activating targets
- Targeted delivery to organs
- Advancement in other types of mRNA to significantly elongate half-life or mRNA, e.g. circular RNA.

BETTING ON MRNA

The above suggest an urgency for making some bets on mRNA technology, particularly for leading players in prophylactic vaccines and immuno-oncology. The ecosystem of mRNA has significantly expanded thanks to the boosting R&D interest driven by the success of COVID.

Exhibit 3: Large Pharma Bets Through Mostly Partnership, While The Recently Bursting New Companies, Offering Potential Future Opportunities For Partnership

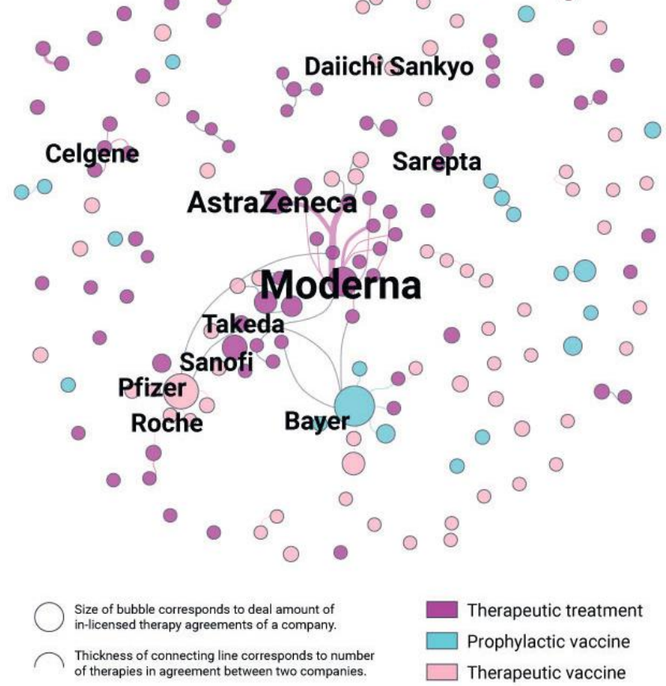


Exhibit 4: Number Of mRNA Specialized Biotech Companies (Cumulative View)

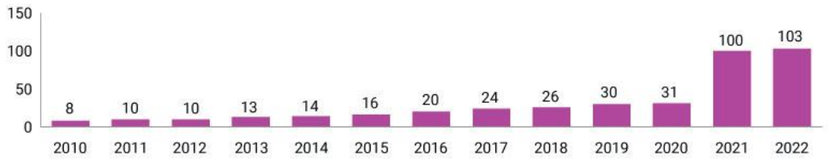
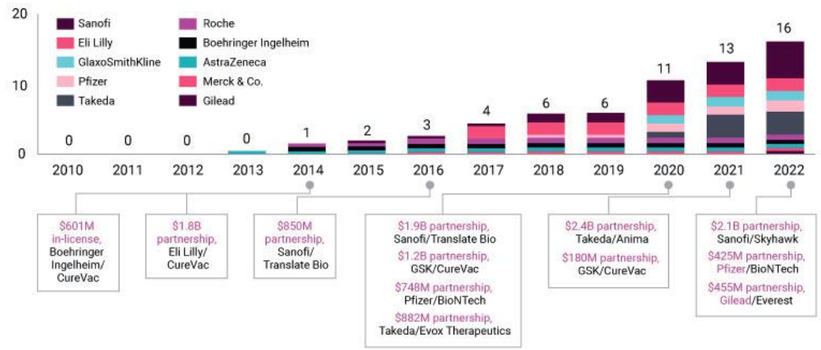


Exhibit 5: Cumulative Deal Value (Upfront + Milestone)[1] Top 20 Pharma Companies And mRNA Companies ($B)



We see new entrants, mRNA specialized biotech and large pharma playing by organic and inorganic moves, forming the complex partnership network. So far big pharma has committed approximately $16bn into research for mRNA therapies in the form of collaborations, license agreements and M&A. The number of companies developing mRNA therapies grew from eight in 2010 to more than 100 in 2022. Going forward, for companies interested in playing in the mRNA market, we see three types of opportunities for betting in the mRNA space:

1). Pipelines Bets A Foot In The Door:
Given the vast amount of possible therapeutic classes and indications to bet on, the first thing companies should decide on is their pipeline portfolio strategy, which should be highly tailored to the company's own aspirations. mRNA's significant potential to deliver on prophylactic vaccines and oncology would enable companies with presence or aspirations in these fields to find significant synergy. We anticipate PCV could become a wave for biopharma immuno-oncology players, upon success in key catalytic events.

The second thing companies need to think of is in-house vs. partnership. When mRNA technology matures and patents start to expire, we could see a wave of biopharma companies deciding to develop their own platforms organically, where a significant portion might be "me too fast following drugs" in synergy with their own IO platforms. However, currently the market cap for the mRNA field is quite concentrated, with two players accounting for more than 90% of the value, implicating on significant technology barrier to play in-house. A leading player merger with a multinational company would seem unlikely, but the rest of the field consists of very early-stage pipelines and platforms indicating many possibilities for collaborations or alliances. As the universe of mRNA players continues to increase, we believe the field will open and there will be partnership opportunities emerging.

2). Eco-System Bets To Work Along The Broader Value Chain:
The wave of "fast-following me too drugs" in the space in four to five years is likely to drive the demand for early sequence development, clinical research organization, and chemistry, manufacturing and control services, as well as intellectual property services , along the value chain. These capabilities require significant amounts of technological foundation and internal know-how, which could take years to develop. Therefore, companies that are holding key patents or participating in the value chain of mRNA development are likely to receive many partnership requests and thus grow over next few years.

Exhibit 6: IP & Know-How Along mRNA Vaccine Development Steps

Key steps	mRNA product design			CMC		
	mRNA sequence generation & screening	mRNA modification	Delivery system design	Plasmid & DNA production	Plasmid & DNA production	LNP formulation
Key activities	• Generate mRNA sequence (by simulation and lab test) • Screen mRNA sequences with best activity	• Modify mRNA sequence (e.g. 5' capping, Poly A tail, uracil replacement) to improve stability & lower unwanted immunogenicity	• Design deliver system to help mRNA remain stable outside the cell and effectively escape after entering cells	• Plasmid DNA production at scale for mRNA generation	• "1-step" or "2-step" reaction for In vitro transcription and capping of mRNA • Purification & QC	• Use microfluidic or T-junction technology to combine naked mRNA and lipids, to mRNA particles • QC of final product
Key IPs	• Patent of mRNA sequence for a certain antigen	• Patent of mRNA modification e.g. -methylpseu-douridine	• Patent of delivery systems e.g. LNP		• Patent of Capping enzyme	• Patent of core equipment
Critical know-how	• Optimize sequence for higher efficacy and expression level	• Optimize to improve stability	• Optimize vehicle components to improve on safety, delivery efficiency and thermostability	• Optimize plasmid structure and process to improve plasmid yield, purity & cost	• Optimize process to improve mRNA yield, purity & cost	• Optimize process parameter to improve PDI & yield in mass production • Dev. microfluidic chip and equip. to reduce cost

1. IVT: in vitro transcription
Source: Expert interview, lit research, BCG analysis

Currently each stage of the value chain is dominated by a few leaders, e.g., Arbutus (Genevant) and Acuitas for LNP patents, TriLink and CleanCap for mRNA transcription and capping, and Precision Nanosystems and Micro&Nano for large-scale LNP CMC. CDMO and life-sciences players (e.g. Moderna partnered up with Lonza, Recipharm, Catalent etc. for mRNA vaccine production) have also provided the mRNA vaccine manufacturing capability at scale. While current players continue to grow, novel players with better technology, lower cost, and larger scale could potentially change the competitive landscape, we believe there may be opportunities to invest in capabilities ahead of the curve.

3). Novel Technologies Bets To Leap-Frog Current Wave Of mRNA:
Companies that have made technological improvements to address critical issues of the mRNA technology will likely attract additional investment, e.g., players focusing on developing circular RNA, or new organ targeted delivery methods. Laronde and ORNA, the two leading global companies focusing on circular RNA, have enjoyed $780m in investment in the past 12 months. In addition, we envision there could be more cross-collaborations among cell and gene therapy players. For example, Intellia (a gene editing company) is developing a bone marrow-tropic LNP which could also be applied to mRNA cancer therapeutics to specifically target hematopoietic stem cells for in vivo T cell engineering. These technologies, if successful, would likely unlock novel mRNA applications towards therapeutics.

In the end, which mRNA strategy a company pursues will depend on current business, the advantage or threat of mRNA to current business or ambition, and willingness to invest in a technology that has a lot of promise but high uncertainty.

Funding The Future: Accelerating The Long Walk To Innovation

Good ideas must be paired with good people

Jo Shorthouse
27 Jun 2022

Executive Summary

In Vivo **spoke with two company creators working in the biotech industry about their strategies for seeking new science and their funding philosophy when building the biotechs of tomorrow.**

Investment in ideas and new science takes research, and often faith to make innovation work. What may be a good idea on paper may not be scalable, or even answer an unmet need for patients. Entering the innovation arena before seed funding and venture capital are companies such as Deep Science Ventures and Oxford Science Enterprises, each taking its own approach to accelerating innovation.

Deep Science Ventures was borne from the philosophy of co-founders Mark Hammond and Dominic Falcão, both previously from Imperial College London's start-up and tech transfer division, that humanity and the planet should be able to thrive together.

Its investment thesis takes the form of an outcomes graph by mapping the various constraints that exist within the company's fields of interest, which include climate, agriculture, computation, and pharma. This outcomes graph guides the company in everything it does by taking a problem-driven first principle approach, thinking of the best ways to reverse-engineer complicated problems and unleash creative possibilities.

THE PARTNERSHIP APPROACH

DSV addresses challenges in a certain area, then partners with external organizations within that given area and hires in a founder (as diverse as recently exited PhDs to serial

entrepreneurs/former CEOs), who decides on the optimal approach to overcome the identified constraints. The founding team is then rounded out and the company is put before the investment committee. DSV holds a stake in each newco it emanates.

"Being able to think holistically about a problem from the get-go makes a difference." - Kerstin Papenfuss

Kerstin Papenfuss is associate director for pharma at DSV and told In Vivo that the beauty of the DSV model is the ability to combine science and engineering in a way that you could not with a traditional tech transfer model at a university. "Being able to think holistically about a problem from the get-go makes a difference," she explained. Previously working at the UK Cell and Gene Therapy Catapult, Papenfuss said that "the companies we start at DSV are considered early, compared to, say, a university spin-out where an established academic has been working on a problem for 10 years. Our edge is that we build companies, drawing on evidence from right across the global landscape."

This ground-up approach has created corporations such as Immtune Therapies, which is working to create a specific gene delivery agent that allows CAR-T cells to grow in vivo with stable expression; Reflection Therapeutics is developing targeted anti-inflammatory cell therapies to reduce neuroinflammation at key sites within a patient's central nervous system; and Ancilia which is developing a new class of engineered bacterial therapies to treat the growing number of diseases linked to the microbiome.

"Our way of working lends itself to spaces where combinations of existing technologies might work and we can bring our scientific engineering expertise to it, where potentially high price therapeutics will be tolerated. So, it must be a

Deep Science Ventures' Kerstin Papenfuss

disease that has a certain severity that might be able to put up with a slightly higher price tag, because it's likely that the solution to a complex disease won't be a simple small molecule or a simple antibody," she explained.

Current partnerships within pharma include Cancer Research UK, the Cystic Fibrosis Foundation and the Cell and Gene Therapy Catapult. These partnerships have already led to three cancer-focussed companies; additional cancer companies, as well as companies focussed on cystic fibrosis and cell therapies, are in incubation.

The DSV approach works well because its partnership model allows it to work with disease charities that are very networked into the networks of academics. For example, the team always begins by talking to key opinion leaders in the field to fully understand the current state of the art. This very detailed understanding of the problem allows the team to ask "naïve questions" of academics such as, in the case of cystic fibrosis, why is the focus on lung delivery of therapeutics when we know that the lung has been designed to keep things at bay? "Within the academic system, you start in a lab and that exposes you to a certain way of thinking and you don't ever get the luxury to ask if this is, fundamentally, the right way of approaching the problem," Papenfuss said.

These conversations have led Papenfuss' team to a systemic strategy for challenging currently untreatable cystic fibrosis mutations. While the four existing CFTR modulators for people with certain CFTR mutations are efficacious, particularly in combination, there is still a significant number of patients with CF who have nonsense and rare mutations who will therefore not benefit from existing therapy.

Papenfuss explained that, with the advances in gene therapy in restrictive and synthetic promoters, this disease can be controlled better than 30 years ago, when we saw the first attempts of tackling diseases with gene therapies. "We ask, if you were to do this systemically, what would you do? What would be your best delivery vehicle? What would you actually express? Can that be done in combination with another vehicle?"

While the DSV model of answering a 'what if' question through company creation is not novel, it believes its partnership model and its internal ideation model is different from other established company creators such as Cambridge, MA-based Flagship Pioneering, responsible for creating 100 science-based businesses including Moderna, Inc.

THE OXFORD APPROACH

Another COVID-19 vaccine recipient of early funding was Vaccitech plc, co-founded by Professors Sarah Gilbert and Adrian Hill, which utilizes T cell mediated immune responses to treat and prevent infectious diseases and cancer. The company was a co-inventor of the Oxford/AstraZeneca Covid-19 vaccine and went public in May 2021. (Also see "Vaccitech Prepares For IPO, But AZ COVID-19 Vaccine Safety Fears Cloud Launch" - Scrip, 13 Apr, 2021.)

Oxford Science Enterprises (OSE) was a founding investor in Vaccitech in 2016 enabling the development of its underlying technology. Since 2015, OSE has received an automatic stake in all Oxford University science spinouts – more than 100 businesses, founded by over 200 of Oxford's leading academics and has actively focused on a core portfolio of 40 companies spanning high growth sectors. Today, collectively its businesses are worth over £2bn and have created more than 2,000 jobs.

OSE's company creation involves applying curated models and playbooks to inspire, accelerate and optimise impact, guided by the scale of the unmet need, the complexity of the science, and its potential.

Like DSV, Oxford Science Enterprises is a company, not a fund restricted by arbitrary fund timelines. "OSE has assembled a group of investors and operators that have a long-term perspective. They understand that they are investing very early and can create a company around an idea. Sometimes there is not even any technology, it's just a concept," explained Katya Smirnyagina, OSE's senior partner, Life Sciences.

Traditional investors are focused on returns and a 10-year exit plan. What further differentiates OSE from the classical venture fund proposition,

Oxford Science Enterprises' Katya Smirnyagina

Smirnyagina said, is that even if a huge financial return is not anticipated the impact to the patient is "a very important component of what we do."

"If we think that a technology is breakthrough, and it will be adopted, we'll go for it. It's a long-term game, and we have the horizon to address it," she explained.

A veteran of venture capital having worked at the sharp end for more than 20 years, Smirnyagina says that the real pressure is not from the typical investor, but from the industry itself, and to make their companies competitive in the market. "It's widely accepted that Oxford has some of the brightest minds. We are here to help them transition their discoveries from an academic lab to an industrial setting. Great minds think alike. If somebody comes up with an idea at Oxford, we cannot rule out that somebody has a similar idea elsewhere. "We are working under an internal pressure to make sure that the companies that we create are competitive," she told *In Vivo*.

WHAT IT TAKES

Smirnyagina looks for opportunities that have the potential to be "transformative for human health." It can be vaccines, small molecules, or biologics. "Our endgame is to find something that will eventually become a drug or a technology that will generate a therapeutic that will be approved by the regulatory authorities to save lives, or improve people's quality of life," she said.

"It's very important to recognize something that really catches your eye, catches your attention."
- Katya Smirnyagina

OSE has a very active outreach program visiting the various academic departments housed at Oxford. Sometimes, she tells In Vivo, the OSE team comes across opportunities that nobody thought could be the basis for a company. "It's very important to recognize something that really catches your eye, catches your attention."

"If a certain academic has five ideas, and s/he thinks that all of them are great, but some of them are more translatable to industrial applications than others. Therefore, it's very important from the start to have this active dialogue and prioritise opportunities with significant commercial potential," explained Smirnyagina.

Having worked for over a decade in the US venture capital market, Smirnyagina would often be frustrated at the apparent lack of biotech funding on this side of the Atlantic. The science was as good, she says, sometimes even better than the science in the US, but the ability to execute on a strategy was not there, something she helps her own investment companies accomplish.

The lack of capital in European bioscience had led to migration of talent to the US, but with sufficient capital, comes the ability to "attract the best people to execute on a certain strategy and build a company going forward. It's as much about people as it is about the technology," Smirnyagina said. "Good people make things happen."

With the current downturn in the markets, this veteran investor believes that, while there will be some "collateral damage", inevitably this rationalization of the industry will be good for all concerned. "At the end of the day, the best companies survive and become more efficient. I think it's a healthy shake out" she said. "There was this tendency, many years ago, to keep companies afloat even though they did not have much potential. They were hoping a miracle would happen. These days stakeholders are more pragmatic."

Micro-Dosing Gene Therapy: A Recipe For Success?

King's College Spinout AviadoBio Is Targeting FTD And ALS

Chloe Kent

27 Jun 2022

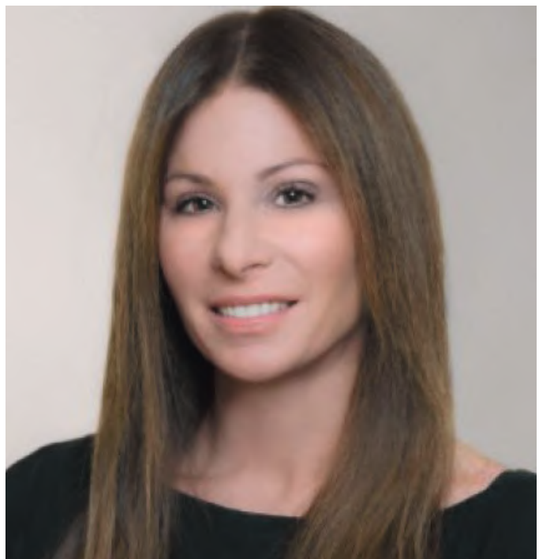
Executive Summary

Utilizing the genetic overlap between frontotemporal dementia and amyotrophic lateral sclerosis, AviadoBio is seeking to develop gene therapies which can stop both these devastating diseases in their tracks using novel delivery techniques.

A significant genetic and pathological overlap exists between frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS), with both diseases recognized as falling across the same neurodegenerative continuum. Up to 50% of ALS patients develop cognitive impairment associated with FTD, while up to 30% of FTD patients develop motor dysfunction. Both disorders can be found within the same family, or even within the same individual, and many genes that were first identified in ALS patients are also present in people who develop FTD.

Given this substantial overlap between the diseases, it is unsurprising that King's College London spinout and gene therapy developer AviadoBio has chosen to target both conditions at once.

"The populations with these conditions are connected," said Chris Shaw, professor of neurology and neurogenetics at King's and AviadoBio's co-founder, chief scientific and clinical advisor. "We've selected patients from each of those disorders that have a particular gene defect to start with, because then you've got a very clear target."



Lisa Deschamps

The company was launched with the completion of an $80m series A financing round in December last year, co-founded by Shaw alongside molecular neurobiologist Youn Bok Lee and vector biologist Do Young Lee, both also of King's College, and the UK Dementia Research Institute (DRI). (Also see "Ex-Novartis Exec Unveils Neurodegeneration Gene Therapy Start-Up AviadoBio" - Scrip, 2 Dec, 2021.)

AviadoBio is using a "novel neuroanatomy-led" approach to drug delivery, utilizing precision micro-dosing of its compounds to achieve gene expression throughout the nervous system. By focusing on both FTD and ALS, overlaps in learnings gleaned from each condition have the potential to benefit both patient cohorts.

The company is still in very early stages, but already boasts some promising pre-clinical data which could see it start to make waves in the central nervous system (CNS) space over the years to come.

AviadoBio CEO Lisa Deschamps said: "If we go back ten years ago, looking at CNS overall, a lot of companies were exiting the space. Big pharma, biotech, everyone, the challenges were just too great. So there haven't been a tremendous number of advancements overall in the last decade, except for maybe neuromuscular with some symptomatic benefits."

"Now we have the opposite going on, where a lot of companies are out there, big and small, trying to go forward and solve the significant unmet needs that exist both on the rare disease side all the way through to the larger disease areas like Alzheimer's and Parkinson's," she told In Vivo "The space looks crowded, but we believe we can be successful."

INTRATHALAMIC PROGRANULIN TO TREAT FTD

AviadoBio's flagship compound, AVB-101, is an investigational, one-time, adeno-associated virus (AAV) gene therapy for patients with FTD who have mutations in the progranulin (GRN) gene which cause it to lose function. AVB-101 is designed to slow or stop disease progression altogether by delivering functional GRN throughout the CNS to restore normal progranulin levels.

The therapy is administered intrathalamically – into the thalamus just above the brain stem – which AviadioBio says facilitates the transportation of the viral vector to the right areas of the CNS to impact disease progression, while minimizing off-target expression and distribution of the protein.

The Lpndon-based company recently delivered some promising pre-clinical data for AVB-101 at the American Society of Gene & Cell Therapy annual meeting. Shaw announced that AVB-101 administration via intrathalamic injection in a progranulin-deficient mouse model had demonstrated neuronal-specific PGRN brain expression and reduction in disease pathology.

Shaw told In Vivo that further pre-clinical animal studies of AVB-1010 have yielded some "extraordinary" results, demonstrating significant delivery of GRN throughout the brains of sheep when the vector was carefully placed at small and set doses. The researchers were also fortunate to not detect any progranulin in the serum or liver after administration of the therapy, which can be associated with negative outcomes such as tumor formation.

Since progranulin is known to be defective in ALS patients too, there is potential for additional exploration of AVB-101 for this indication in the future – something which is also true of the other therapies in the company's pipeline.

Significant interest currently surrounds the use of AAV gene therapies for dementia, with few conditions falling under the umbrella having any effective pharmacological treatment available. The DRI recently teamed up with the UK Cell and Gene Therapy Catapult to seek out high-potential dementia gene therapy projects. The collaborators will create detailed development plans for each project and potentially conduct early research activities to prepare assets for further investment.

GENE KNOCKDOWN IS REQUIRED FOR TOXIC TRAITS

Alongside AVB-101, AviadoBio is working on two undisclosed gene knockdown projects targeting both ALS and FTD.

"Most of the genes that cause ALS are toxic," Shaw said. "No amount of supplementing is going to help, so we need to just knock those genes down. We've developed a novel mRNA silencing construct, a gene which if placed into a virus is expressed in the very long term as well. We've got really, really fantastic knockdown in cellular models and we're now taking this forward into animal models."

Chris Shaw

For these therapies AviadoBio is pursuing a different means of delivery, injecting the compounds into the spinal cord rather than into the thalamus deep inside the brain.

Shaw explained: "Although we've got fantastic distribution in the brain from our thalamic injections, we don't get much delivery to the spinal cord. We're collaborating with a wonderful man in San Diego who has a device which allows us to inject into the spinal cord in a fantastic way, just under the pia membrane. We're able to transduce, possibly, 80% to 90% of all neurons in the spinal cord."

This method of administration, he emphasizes, is very different to what some of AviadoBio's competitors are doing, administering gene therapies to the blood or spinal fluid. Both methods can ultimately lead to viral vectors winding up in the liver, where they are unable to exert a therapeutic effect.

"Relatively few people have taken gene knockdown forward to the clinical stage," Shaw said. "I think it's a very, very powerful area, because you could tackle not just single gene disorders but toxic gain-of-function. There are various pathway modifications you can use by knockdown which might be beneficial for people with spreading disease, and we've got some indications with ALS and FTD which could have a very profound effect on all patients with these conditions, and not just those with a specific genetic defect."

THE ROAD TO COMMERCIAL VIABILITY

For many gene therapy companies, the real challenge comes following their demonstration of success in the lab, when they attempt to bring their product to market. Fortunately for AviadoBio, Deschamps brings 25 years of industry experience with her to the company, having previously worked at Novartis Gene Therapies as senior vice president and chief business officer. Deschamps' experience includes the worldwide commercial launch of Novartis's breakthrough gene therapy for spinal muscular atrophy Zolgensma (onasemnogene abeparvovec).

Zolgensma was a hugely significant entrant into the CNS gene therapy field. The one-time treatment targets the genetic root cause of spinal muscular atrophy, replacing the missing or non-working SMN1 gene with a new, working copy of the SMN gene. Novartis was also able to make the therapy a commercial success, despite its high upfront cost of around $2.5m per dose. (Also see "Novartis Steers Zolgensma Towards Commercial Success In Europe" - Scrip, 12 Mar, 2021.)

AviadoBio may also find its efforts bolstered by the fact that US and EU regulatory authorities have both said they want to help make the approval process for the sector more straightforward. (Also see "FDA Leader: We Need To Remove Surprises From Gene Therapy Development" - In Vivo, 6 Jun, 2022.)

Deschamps told In Vivo that AviadoBio had had "good engagement" with the US Food and Drug Administration, European Medicines Association and the UK's Medicines and Healthcare products Regulatory Agency, as well as "starting to engage with other regulators around the world."

"At the end of the day, what is most important is being proactive on the engagement side and making sure you're moving forward lockstep with the policymakers, the regulators, the reimbursement bodies."

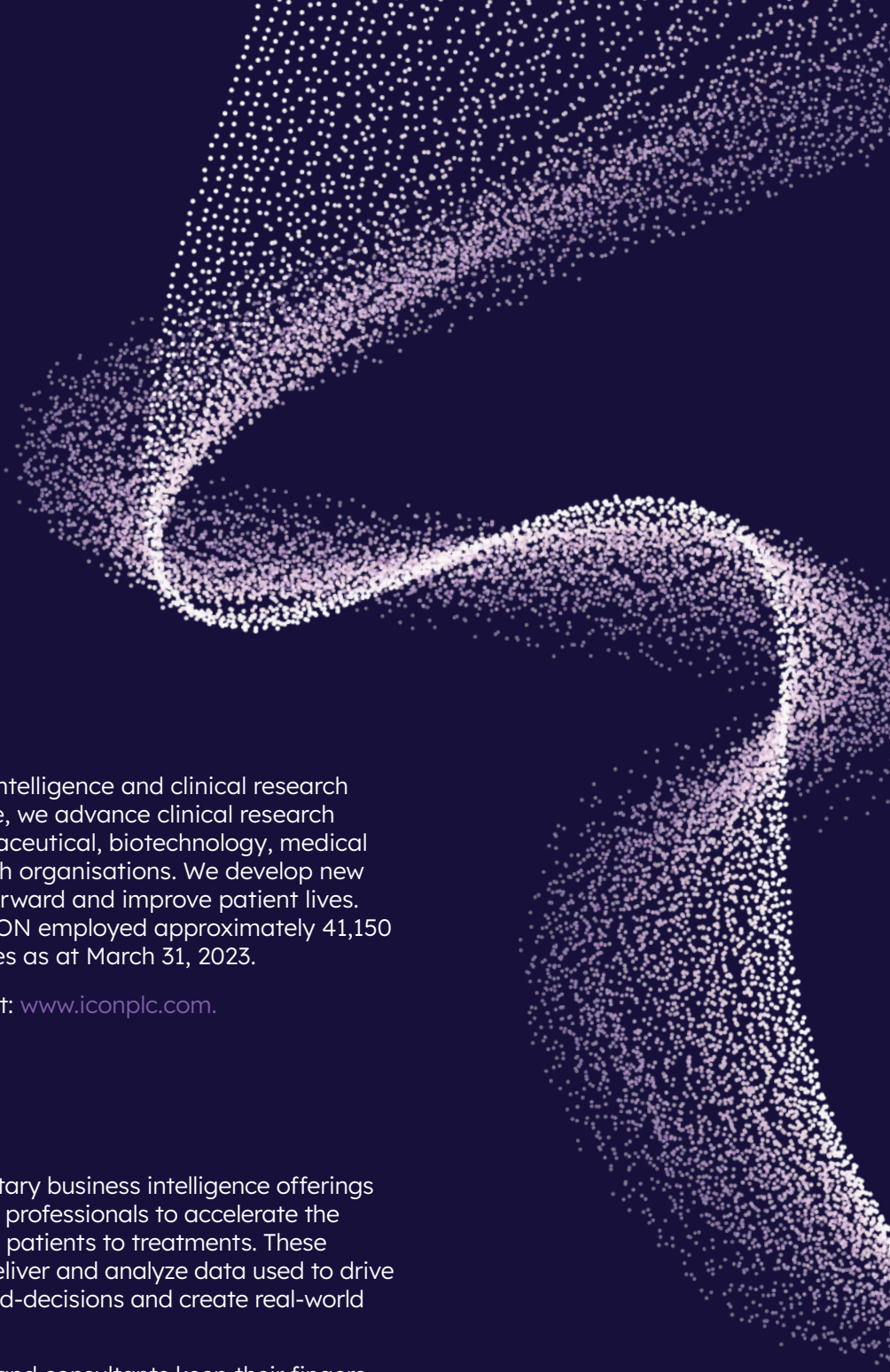
She said: "At the end of the day, what is most important is being proactive on the engagement side and making sure you're moving forward lockstep with the policymakers, the regulators, the reimbursement bodies."

She continued: "We announced that we'd raised $80m at the end of last year, and that money is really focused on driving forward our early program in FTD as well as advancing the rest of our pipeline to get as close to the clinic as possible. We feel really confident that the money raised will be able to help us do that successfully within the next couple of years."

AviadoBio currently plans to enter the clinic before the end of the year and is now engaged in IND-enabling studies which it anticipates will read out "in the relatively near future."

For now, the company says it is "hyper focused on advancing our programs into the clinic and beyond" and will "formulate the appropriate strategy for commercialization that maximizes the opportunity to enable access for patients" as it moves forward. Should its micro-dosing methods prove as effective in human trials as they have in cellular and animal models, then these novel mechanisms of action could be the first chapter in a CNS success story.

CITELINE
COMMERCIAL



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