The death cap mushroom (*Amanita phalloides*) produces cell toxins that are now being tested in the clinic as ADCs. Results are expected soon.

Cancer: Hit it with your best shot

THERAPEUTICS After decades of development, antibody-drug conjugates (ADCs) are increasingly making headlines, although the earliest authorisations were somewhat less successful than theory predicted. Researchers now finally appear to be mastering the interplay between antibody, linker and toxin. The next wave of ADCs is just around the corner

When the first antibody-drug conjugated co-therapy was approved, euphoric observers viewed it as a breakthrough. Modified ADCs loaded with a cytotoxic payload have long been a goal in the field. The initial hopes proved to be misplaced, however, and practical experience has since revealed that the fragile complex of a protein-chain antibody – usually coupled to a cytotoxin via a linker – interacts with the body's physiology in ways that are still far from being sufficiently understood. If toxins detach from their antibody transport system too early and unspecifically, it can affect healthy cells and tissue close to the targeted tumour. This 'collateral damage' could mean high toxicity, and was a fundamental reason the first wave of approvals disappeared from treatment schedules.

The first ADC to be approved back in 2000 was Mylotarg, which was pulled from the market in 2010 because death rates actually increased under medication. It was relaunched in 2017, but meaningful traction really only set in when the technology for each component improved and second-generation ADCs were introduced, among them Takeda's Adcetris in Hodgkin lymphoma (2011) and Genentech/Roche's toxin-coupled variant of trastuzumab, Kadcyla (2013). Since then, clinical and commercial wins have continued to rack up, including for programmes combining ADCs with checkpoint inhibitors (i.e. Padcev/Keytruda).

The field of developers has subsequently split even more into those specialised in coupling the toxin to the antibody and those who test and optimise a range of cytotoxins from nature – or known chemotherapy cytostatics – in tissue-specific delivery to the tumour. A smaller fraction of companies and development projects in Big Pharma companies is focused on antibody variants, along with smaller fragments and their various modifications, to see whether they could be made even better at specifically delivering toxins to a desired target site, generally due to better penetration of tumour tissue.

Good ideas can take time

But smaller antibody derivatives have not yet proven to be more successful than their larger cousins. Faster degradation rates and other pharmacokinetic dynamic factors could be reduced with a number of space-taking attachments, but this also appeared to reduce penetration into tumour tissue – a hoped-for advantage of smaller fragments.

Experienced developers on the ADC front have now told European Biotechnology that the years of research have helped to clarify many outstanding issues. Specialisation in linker technology and cytotoxins has brought a lot of progress, while many licensing deals and acquisitions can now be seen in the area. Some were the subject of discussion at major partnering events like BIO-Europe 2023, which took place this time around in Munich.

Deals that are making headlines

The ADC space has heated up in a big way in the last few years. Over US$125bn in partnerships and M&A have been reported since 2019, including this year's Pfizer US$43bn mega-acquisition of Seattle Genetics (Seagen) and a record US$5.5bn upfront deal between Merck (MSD) and Daiichi Sankyo. There are hundreds of assets across thousands of trials in the field in various indications. Eight approvals in the last five years (raising the number to 13 in total) have done more than crack open the door. Looking at pipelines and assets in later clinical phases, it seems more like a dam has broken. If you include the radiopharma space in the ADC landscape as well, as a closely related technology for delivering killing substances spatially in cancer, an overview of what is going on where becomes even more entangled.

Active players in the ADC arena are depicted in the table on the next page.

But what is actually happening can only be explored here in part. That said, let's look at some notable deals and individual companies that, although small, are trying to approach the area in sustainable ways.

That's a tough thing to do in an era when small companies are often swallowed up by Big Pharma before they even really get up and rolling. Eli Lilly, for instance, seems to be buying everything that's not nailed down at the moment. Its acquisition of Emergence Therapeutics has already caused a stir in the ADC space. No figures were given for the deal, but it can only be assumed that the sums involved are in the high triple-digit million range. The acquired Franco-German firm had a spectacularly short independent life, with headline-grabbing start-up financing. Founded in 2019, Emergence Therapeutics really started to appear on industry radars at the end of 2021 with an impressive Series A financing round of US$94m (around €87m at the time). Initially founded in Marseille (France) and located in Duisburg (Germany), the company was able to bring

An incomplete (due to dynamics) list of European biotechnology and pharma companies active in the ADC space

Company	Country
Valanx Biotech GmbH	Austria
Precirix N.V.	Belgium
UCB S.A.	Belgium
Sotio a.s.	Czech Republic
Adcendo ApS	Denmark
Genmab A/S	Denmark
Mablink Bioscience S.A.S. /Eli Lilly	France
OSE Immunotherapeutics S.A.	France
Pierre Fabre Group	France
Sanofi	France
Seekyo Therapeutics Inc.	France
Servier	France
Bayer AG	Germany
BioNTech SE	Germany
Boehringer Ingelheim GmbH	Germany
Emergence Therapeutics AG/Eli Lilly	Germany
Glycotope GmbH	Germany
Heidelberg Pharma AG	Germany
ITM Isotope Technologies Munich SE	Germany
medac GmbH	Germany
Merck KGaA	Germany
Tubulis GmbH	Germany
Veraxa Biotech GmbH	Germany
Mundipharma International Ltd.	Ireland
Biond Biologics Ltd.	Israel
Nectin Therapeutics Ltd.	Israel
Teva Pharmaceutical Industries Ltd.	Israel
MediaPharma S.r.l	Italy
Menarini Group	Italy
Philogen S.p.A.	Italy
Byondis B.V.	Netherlands
Tagworks Pharmaceuticals B.V.	Netherlands
Nordic Nanovector ASA	Norway
Ryvu Therapeutics S.A.	Poland
Genagon Therapeutics AB	Sweden
Immedica Group AB	Sweden
Oncopeptides AB	Sweden
Swedish Orphan Biovitrum AB	Sweden
ADC Therapeutics S.A.	Switzerland
Araris Biotech AG	Switzerland
Debiopharm Group	Switzerland
GlycoEra AG	Switzerland
Lonza AG	Switzerland
Novartis AG	Switzerland
Roche	Switzerland
Abzena Ltd.	United Kingdom
Almac Group Ltd.	United Kingdom
AstraZeneca plc	United Kingdom
Avacta Group plc	United Kingdom
BiVictriX Therapeutics plc	United Kingdom
Cancer Research UK	United Kingdom
Elasmogen Ltd.	United Kingdom
GSK plc	United Kingdom
Hikma Pharmaceuticals plc	United Kingdom
Iksuda Therapeutics Ltd.	United Kingdom
NanoMab Technology Ltd.	United Kingdom
Oxford BioTherapeutics Ltd.	United Kingdom
Pheon Therapeutics Ltd.	United Kingdom

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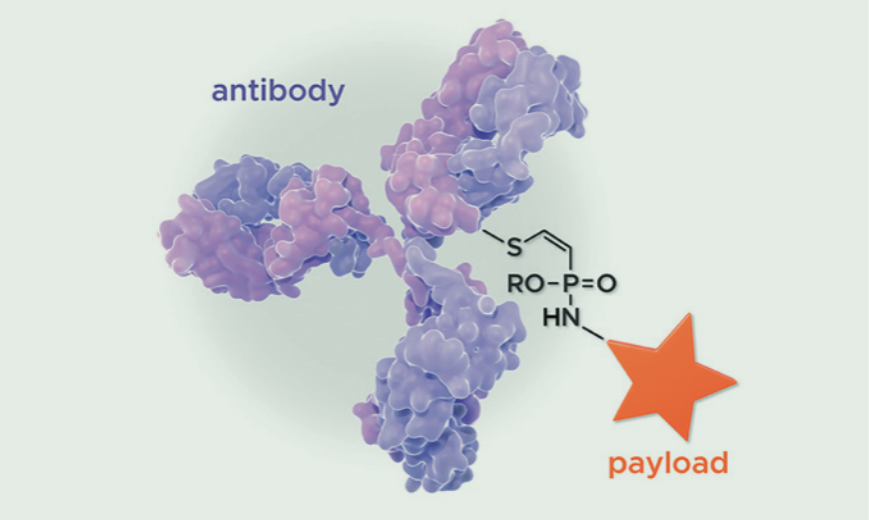

Different linkage technologies promise different results

numerous French investors on board, but also attracted Rhineland-based investors like NRW.BANK, High-Tech Gründerfonds and Gründerfonds Ruhr in addition to French investors such as Kurma Partners and Bpifrance. Its single asset and target-specific approach led investors to throw money at Emergence, and encouraged Eli Lilly to buy it. The start-up's most mature candidate (ETx-22) targets Nectin-4, a membrane surface protein commonly found on malignant cells but rarely expressed by healthy cells. This antigen has recently been clinically validated by the approval of Astellas and Seagen's Padcev (enfortumab vedotin), another ADC that targets Nectin-4 for urothelial cancer. In October 2021, Emergence obtained the rights to develop the novel compound using Mablink Bioscience's proprietary PSARlink drug-linker technology. Using the proprietary linker and payload technology, Emergence was developing ETx-22 to be a next-generation, Nectin-4-targeting ADC that can deconjugate from tumour cells and thus reduce side effects such as skin toxicities, which is particularly dose-limiting for Padcev. According to the company, the technology allows for higher doses of ETx-22, thereby increasing its efficacy without triggering more safety concerns.

Eli Lilly's next acquisition in the space seemed like a no-brainer: the US pharma bought French firm Mablink Biosciences, which can obviously add value to asset companies by providing a specific linker technology. Once again, numbers in the acquisition have been kept secret until final approval by different state legislatures – expected in a few weeks – is given. But guesses are that the purchase will surpass the Emergence deal, as Mablink's PSARlink™ is a multipurpose innovative hydrophilic linker using a polysarcosine arm, and could potentially broaden the therapeutic index of many ADCs to come, unleashing their full therapeutic impact.

More in the linker space

Other linker companies are also very much in the spotlight. German-based Tubulis for example, with founders from Berlin and Munich based at the Martinsried IZB start-up centre, was able to enjoy spectacularly high financing rounds (especially for Germany) with €60m from VCs like Andera Partners, Seventure Partners, BioMedPartners, Occident and others, but also preclinical drug developer Evotec SE from Hamburg in 2022. This may be due to the small company's goal: maximising the *overall* performance of ADCs. Company CEO Dominik Schumacher characterises their vision as a "mission to address the main bottlenecks in the field and innovate the ADC from

Picture: ©Tubulis GmbH

all sides, not only the linker. The linker is a core element of the ADC and the efficient binding between chemical agent and antibody is an important step in creating improved ADCs," he adds. "But focusing on the linker alone is not sufficient to realize the full potential of ADCs. This is the reason we also focused on improving the payload and the antibody early in the evolution of Tubulis." The firm's technology platform, with expertise and know-how extending to both ends of the linker – payload and antibody carrier – has not only sparked interest among venture capitalists, but is also the foundation stone for a huge collaboration deal closed earlier this year with Bristol Myers Squibb.

In addition to the deal's upfront payment of US$22.75m, future instalments totalling up to US$1bn could come if different milestones are reached. The partnership gives BMS exclusive access to Tubulis' proprietary P5 conjugation platform and tubutecan payloads for the development of a selected number of versatile and customisable antibody drug conjugates for cancer therapy. The platform enables the generation of ultra-stable ADCs that have the potential to actively reduce unwanted off-target toxicities and are optimised for the targeted delivery of potent topoisomerase-1 inhibitors – sought-after candidates after the billion-dollar Merck/Daiichi Sankyo deal. The Japanese company brought this class of toxins via ADC to approval, and have several more in late-stage clinical testing.

Others are now looking for assets and technology to grab at least a slice of the pie in the topoisomerase-1-inhibition race. Tubulis' new partner Bristol Myers Squibb (BMS) will assume sole responsibility for the development, manufacturing and commercialisation of any resulting ADC candidates. "This strategic agreement with BMS is an important validation of the potential of our approach in developing next-generation ADC-based therapeutics and our cutting-edge ADC conjugation technologies that accommodate advanced ADC design to tackle tumours with high unmet medical need," said Schumacher, adding that "collaborations and partnerships are part of our business model and we will continue to explore opportunities that fit into our strategic development plan. We have built a broad suite of proprietary technologies that allow us to combine different antigen-binding molecules, linkers and payloads with unprecedented stability. This enables us to open completely new avenues to apply ADCs, and provides us with a significant level of flexibility."

CDMOs in the house

A lot depends on the parameters of a specific linker technology, and being a technology company makes it easier for a larger corporate to pick up and integrate a firm into its own portfolio. A rather remarkable deal in this area was made by CDMO Lonza in the ADC space. The Swiss company recently bought Synaffix, a company with expertise in linker technology, in order to explicitly extend its well-known production expertise as a CDMO to the ADC area. It even wants to become a kind of one-stop shop for developers of antibody drugs who are considering achieving an even greater tissue-specific effect with an additionally coupled cytotoxin and/or at the same time looking to convince investors with a product variant. Lonza could thus step out of the production partner segment, placing one foot in a new area as a development partner and acquiring its own (purchased) expertise in drug conjugation. In the words of Lonza, the new addition of the Dutch firm to the portfolio – different award-winning platforms in linker-conjunction with sugar – will combine Lonza's development and manufacturing capabilities with the Synaffix ADC technology platform and "will provide customers and licensees with a comprehensive service to rapidly discover, develop, scale-up and commercialise novel and differentiated ADCs." These enhanced capabilities are meant to streamline the path to clinic and commercialisation. Whether Lonza will add further ADC building blocks to its portfolio is still up in the air – as is the strategy of shifting a contract manufacturing business' focus to an early

stage in drug design, offering added value. Will it find resonance in the community and with customers and manufacturers? Only time will tell.

What you link is what you get

Like the 'linkers', the field of 'cytotoxers' has also broadened considerably. Approved drugs are spread out over a range, but four out of 13 of them carry monomethyl auristatin E or F (MMAE or MMAF). Those are toxins that inhibit cell division by binding to tubulin dimers and disrupting the microtubule network. Two approved ADCs that use inhibitors of topoisomerase-1 have opened a new path for payload attractiveness, and topoisomerase-2 is also in the crosshairs. What comes next? Will it turn out to be nothing more than playing with Legos? Clicking together the ADC components of choice, then hitting the clinic?

Another German company that has been active in this field for long time, Heidelberg Pharma AG, has pointed out that despite the seemingly modular nature of ADC components – antibody, toxin, linker – what's decisive is the resulting molecule as a whole. Its physicochemical and pharmacological properties are not just the sum of the individual pieces. They can't be reliably predicted beforehand, and can only be fully understood through testing and analysis. That is the most time-consuming aspect of drug development in any area, as laboratory and *in vivo* models provide only an approximation of the disease and drug effects in patients, and the physiology of humans can only be understood in humans.

Andreas Pahl, CSO at Heidelberg Pharma (HDP), explained his company's strategy as aiming not only to be expert with individual ADC components like linkers, antibodies or cytotoxic payloads, but as positioning itself as a drug development company with substantial ADC expertise. The ADC field is becoming increasingly competitive as Big Pharma acquires many technologies or entire companies in the area. By adding this know-how to their pipelines and combining it with their clinical and disease expertise as well as extensive resources, they are usually able to bring drug candidates to approval more frequently and faster than a single-asset company.

Clinical proof is within sight

Although the area sees busy Big Pharma entering at various stages, Pahl sees advantages for smaller companies like Heidelberg Pharma with a growing pipeline: if they can deliver the research and development expertise built up over years and decades to the ADC space at just the right time. And he sees the time as ripe for yet another payload that has been in development for a long time and is ready to top up the toolbox once the run for topoisomerase inhibitors has cooled down: RNA-polymerase II inhibitors, like alpha-amanitin, derived from the death cap mushroom (*Amanita phalloides*). "If it takes that long, everyone thinks you have problems. But even Daiichi took 15 years before the breakthrough came. At HDP, we are now right on the cusp of being able to deliver this clinical data for our lead programme in the next half year," he told European Biotechnology. Pahl added: "We are entering the right time window for our ADCs and we have built up very good patent protection for Amanitin and the respective biomarkers for many years to come. Yes, we are a 'single player' with this payload, which is always a risk. But our first-in-human trial, which is currently in the dose-finding phase, has been going well and we are already receiving expressions of interest from pharma. So it's really very exciting at the moment."

Everything depends on data from the clinic. Dominik Schumacher, with a preclinical pipeline at Tubulis, is aware of this: "Our main focus," he emphasised, "is currently to further advance our pipeline of ADC candidates towards clinical evaluation." Even with help from others: Oncoteq AG (Switzerland) just entered a global partnership on a CD30-ADC from Tubulis. ■

g.kaeaeb@biocom.eu