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# FDA approves 100th monoclonal antibody product

Thirty-five years on from the FDA's approval of a first monoclonal antibody, these biologics account for nearly a fifth of the agency's new drug approvals each year.

*Asher Mullard*

In the mid-1970s, immunologist Stuart Schlossman had a lab space problem. In order to unravel the ins and outs of T cell biology, he was working with a then-new and revolutionary method for purifying monoclonal antibodies. The hybridoma technique — which Georges Köhler and César Milstein won a Nobel prize for in 1984 — involves inoculating mice with antigens, extracting spleen cells, fusing these with cancer cells and then growing up the immortalized antibody-secreting B cells. For Schlossman, that would mean lots and lots of plates of cells in his Harvard Medical School lab. "We were worried that we just wouldn't have enough room in our incubators to keep all the cultures going," he recalled, four decades on.

Schlossman struck a discovery deal with Ortho Pharmaceutical — a subsidiary of Johnson & Johnson — to secure more incubator space. This partnership would prove short-lived and end acrimoniously, but it set the wheels in motion for a whirlwind development programme and the early arrival of antibodies as a therapeutic modality.

By 1979, Schlossman and his collaborators had identified three monoclonal antibodies against distinctive T cell antigens. One of these, dubbed OKT3, targeted a then-unnamed antigen that is now called CD3, a cell-surface protein complex with a key role in T cell biology. The researchers quickly realized that OKT3 could be used to deplete T cells, and by 1981 they were testing OKT3 in the clinic as an immunosuppressive for the prevention of transplant rejection. In 1986, OKT3 — then renamed muromonab-CD3 — secured a first therapeutic monoclonal antibody approval from the FDA.

"It was an explosive time," says Schlossman. "Everything we touched was gold."

The rest of the field took a little longer to catch up. The FDA didn't approve a second therapeutic monoclonal antibody product until 1994, 8 years later. And antibody approvals have only been an annual event since 2006 (FIG. 1). Now the modality is taken for granted, with an average of around ten approvals per year. The FDA approved its 50th antibody in 2015, 29 years after the first one. It took just 6 more years to reach number 100, with the approval of GlaxoSmithKline's PD1 blocker dostarlimab in April.

For drug developers advancing other modalities — including antisense oligonucleotides, mRNA-based drugs and targeted protein degraders — this is the timeline to beat.

The commercial power of antibodies is even more evident. In 2019, antibodies accounted for 9 of the 20 top therapeutics by sales, show data from the Cortellis database. These 9 antibodies had cumulative earnings of US$75 billion that year.

The number of antibodies entering the clinic is meanwhile increasing rapidly.

"Holy cow, things are just going great guns now," says Janice Reichert, Executive Director of The Antibody Society.

## On-target activity

The appeal of monoclonal antibodies has long been clear. They offer exquisite specificity and affinity for both secreted and cell-surface targets. Different formats of antibody (FIG. 2) can be used to mop up circulating proteins, to block signalling pathways outright, to drive the internalization and degradation of cell-surface receptors, to deliver small-molecule payloads to specific cell types, to recruit immune cells to cancer cells, and more. Whereas medicinal chemists can toil for years to find small molecules with activity against a given target, antibody discovery can take a matter of months. And with a 22% overall success rate from phase I to approval, according to Reichert's analysis of 569 antibodies that entered the clinic between 2005 and 2014, antibodies are twice as likely to succeed in trials as small molecules.

Drug developers, as a result, have embraced antibodies.

But despite having now reached a landmark 100th approval, the target space these approved biologics cover is more limited. Just ten targets — counting ligands and their receptor pairs together — account for 42% of the approvals to date (TABLE 1). Topping the list are the PD1/PDL1 immune checkpoint inhibitors, with seven approvals (now tied

> Holy cow, things are just going great guns now

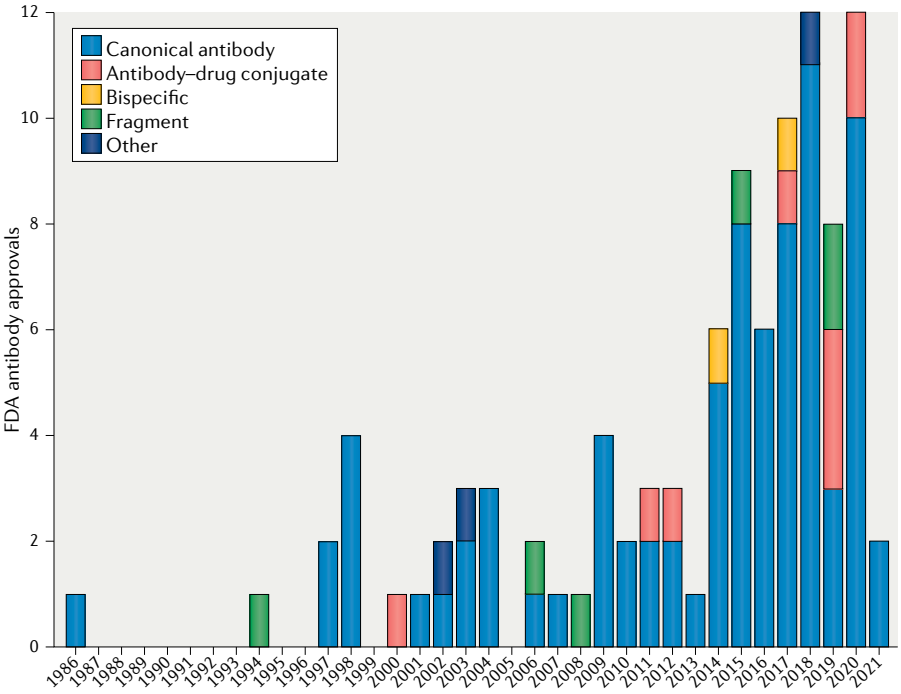


Fig. 1 | **The FDA's first 100 antibody approvals, by year.** Antibodies that span multiple formats have been classified on the basis of their primary functionality. Amgen's blinatumomab, for example, is classified as a bispecific rather than as a fragment. Fragments include antigen-binding fragments, single-chain variable region constructs and domain antibodies. Other includes radiolabelled antibodies and antibody–immunotoxins. See FIG. 2 for more discussion of the formats. Sources: The Antibody Society, *Nature Reviews Drug Discovery*.

with the lipid-lowering small-molecule statins on the approval front). B cell-depleting CD20-targeted antibodies have meanwhile secured six approvals.

"I'm not sure that this is surprising. That's what pharma often does," says Paul Parren, head of R&D at Lava Therapeutics and a prior head of preclinical development at Genmab. When companies see that something works, they want to make something better, he says. "It's a fair approach," he adds.

It helps that some of the pioneering products for the most crowded targets have been game changing for patients, and particularly lucrative. Immunotherapeutic PD1/PDL1 blockers, first approved in 2014, can for example drive lasting responses in various cancers. Merck & Co.'s PD1 blocker pembrolizumab earned more than $11 billion in 2019, and could make as much as $24 billion by 2025. Bristol Myers Squibb's PD1 blocker nivolumab earned $8 billion in 2019 and is expected to pass the $10 billion threshold shortly.

The rush for PD1/PDL1-targeted antibodies also reflects an expectation that these agents will be a backbone component of many cancer drug regimens. "We invested a lot of time in generating our own PD1 antibody … so that we would have our own foundational drug that we can combine with different types of drugs," says Dimitris Skokos, Senior Director of Cancer Immunology at Regeneron. With an in-house checkpoint inhibitor in hand, he explains, Regeneron can explore options on its own terms.

A handful of immunosuppressant targets have also been especially successful. AbbVie's disease-modifying antirheumatic biologic adalimumab, a TNF-targeting antibody, is currently industry's top-selling drug. Approved in 2002, it earned nearly $20 billion in 2019. Johnson & Johnson's anti-TNF infliximab, approved 4 years before adalimumab, peaked at $10 billion in annual sales in 2015 but still earned more than $5 billion in 2019.

With first movers trying to protect profitable autoimmune franchises, and newcomers vying for these markets, TNF and IL-6 signalling pathways have notched up four antibody approvals each.

There is similarly plenty of clumping in the clinical pipeline, show data from The Antibody Society. There are now nearly 870 antibodies in clinical development, but about 36% of these act on another short list of just ten validated and novel targets (TABLE 2).

Some of the follow-on efforts reflect the development of antibodies for a big Chinese market. In other cases, validated targets are being pursed anew, with bispecific or other formats that offer novel activity profiles. But nevertheless, PD1/PDL1, HER2, CTLA4, EGFR and CD20 remain over-represented in the antibody pipeline. PD1 and PDL1 together account for just under a tenth of the experimental pipeline. CD3 is close behind, but targeted now by bispecifics to recruit T cells to cancer cells, rather than to deplete T cells.

Novel, competitive targets in development include 4-1BB, LAG3 and CD47.

As such, cancer is set to continue to dominate in the antibody space (FIG. 3, 4). Despite recent pioneering approvals in cardiovascular disease, with PCSK9 blockers, and neurology, with the CGRP blockers, cancer remains ascendant. Up until 2014, drug developers advanced roughly the same number of cancer and non-cancer antibodies into the clinic each year. In the past 5 years, however, cancer programmes have pulled ahead. In 2020, for instance, more than twice as many cancer programmes entered the clinic as non-cancer programmes (106 versus 51).

This trend is also driven in part by Chinese firms developing antibodies for a Chinese market, says Reichert.

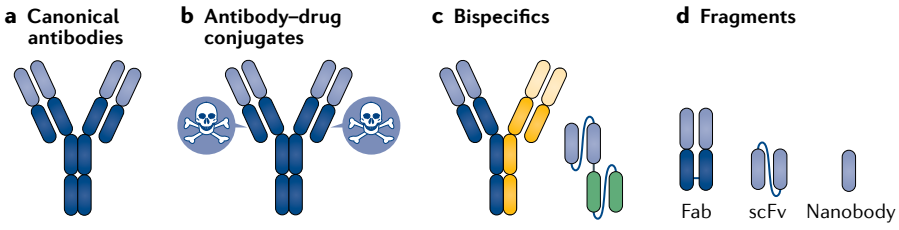


Fig. 2 | **Antibody formats.** Antibody formats include canonical (part **a**), antibody–drug conjugates (part **b**), bispecifics (part **c**) and fragments (part **d**). Fragments include antigen-binding fragments (Fabs), single-chain variable region (scFv) constructs and domain antibodies. Radiolabelled antibodies and antibody–immunotoxins are not shown. These formats can be further subcategorized, and antibodies can span classifications. There are at least 30 different bispecific formats, for example, some of which include fragments. Modified from *Nature Reviews Drug Discovery*.

Table 1 | **Top targets for first 100 mAbs**

| Target | mAb count |
|---|---|
| PD1/PDL1 | 7 |
| CD20 | 6 |
| TNF | 4 |
| HER2 | 4 |
| CGRP/CGRPR | 4 |
| VEGF/VEGFR | 4 |
| IL-6/IL-6R | 4 |
| IL-23 p19 | 3 |
| EGFR | 3 |
| CD19 | 3 |

mAb, monoclonal antibody. Sources: The Antibody Society, *Nature Reviews Drug Discovery*.

With the arrival of COVID-19, infectious disease applications got a bump. More than 20 SARS-CoV-2-targeted products are in the clinic, launching the pathogen's spike protein onto the list of the top ten targets. Several of these have secured Emergency Use Authorization from the FDA, but not full approval. It remains to be seen, however, whether interest in infectious diseases will persist. "I think things will just revert right back to cancer, frankly," says Reichert.

Tillman Gerngross, CEO of Adimab, is optimistic that drug hunters will increasingly break from the crowd, however. Adimab, an antibody service company, has run more than 360 antibody discovery campaigns for more than 80 partners. In the early days of the cancer immunotherapy stampede, he watched these partners chase the same targets. "It was a little bit of a concern, because we thought, 'this is going to end at some point, what's going to come next?'" recalls Gerngross.

With the barriers to antibody discovery falling, however, biotechs and academics have realized that the modality offers a quick and efficient way to explore biology. "It's getting more diverse for sure" as more people embrace these biologics, says Gerngross.

For its part, 14-year-old Adimab spun out its first start-up last year, launching Adagio to advance a homegrown antiviral antibody into the clinic. Adagio's focus is on infectious diseases, taking on SARS-CoV-2, SARS-CoV and other pre-emergent coronaviruses.

## A smorgasbord of flavours

Approved and experimental antibodies come in a wide array of formats, some of which span classifications (FIG. 2).

The bulk of the approved products to date are 'canonical' biologics, antibodies that look pretty much like they would in their natural state. Canonical antibodies — comprising human, humanized, chimeric and murine antibodies — account for 80% of the FDA green lights to date. They are also responsible for the majority of the modality's commercial success. Of the top 20 antibodies by sales, 19 are canonical antibodies (TABLE 3).

The definition of a canonical antibody, however, is increasingly blurring. Whereas Ortho advanced OKT3 straight from a discovery experiment to the clinic decades ago, antibody engineering is now the norm. It provides a means of controlling a candidate's half-life, affinity, biological function and safety. "I used to keep track of things like what was glyco-engineered or Fc-engineered, and all that kind of stuff. But that's become so common now that it's not even worth paying attention to," says Reichert.

Other formats are also on the rise. Antibody–drug conjugates (ADCs), for example, consist of an antibody fused to a drug. For the most part, these are used to deliver toxic small molecules directly to cancer cells. The FDA approved a first ADC, Pfizer's CD33-targeted gemtuzumab ozogamicin for acute myeloid leukaemia (AML), in 2000. The agency has now approved a total of ten ADCs — including ADC Therapeutics's loncastuximab tesirine, the 101st antibody, approved by the FDA one day after dostarlimab. It has approved six of these ADCs since the start of 2019.

This recent surge in ADC approvals, however, belies the turbulence these biologics have faced. "Early on, we went pretty strong into ADCs. Preclinical experiments were stunning," Pfizer CSO Mikael Dolsten told *Nature Reviews Drug Discovery* last year. "But we've learned that only a fraction of these translated into human disease."

Moreover, only two ADCs — Genentech's trastuzumab emtansine and Seagen's brentuximab vedotin — have broken past $1 billion in sales. And next-generation conjugation strategies and more toxic payloads have struggled to overcome the format's translational pitfalls.

As recently as 2017, for instance, ADC experts hoped that more toxic payloads combined with site-specific conjugation strategies would yield more potent, more homogeneous and more stable agents. Seagen's vadastuximab talirine, a CD33A-targeting ADC for AML, was the phase III poster child of these 'third-generation' ADCs. In June that year, the company discontinued the candidate owing to the increased incidence of death with this agent. It subsequently shuttered four related programmes that used the same linker–payload technology.

> You have to be pragmatic, and discuss these programmes with oncologists and physicians

Older ADC technologies have, by contrast, outperformed. Pfizer withdrew gemtuzumab ozogamicin from the market in 2010, after confirmatory trials in AML did not find evidence of clinical benefit. Pfizer then retested the ADC in the same setting but with a different administration schedule and saw benefit. The FDA reapproved the ADC in 2017.

Gilead, meanwhile, paid $21 billion in 2020 to acquire Immunomedics and its approved TROP2-targeted ADC sacituzumab govitecan. This ADC has a relatively low potency warhead, and a non-stable linker that leaks drug, killing untargeted cells. Such profiles were once shunned by ADC developers, who thought that high potency and high stability were the key to success. But sacituzumab govitecan's efficacy in triple-negative breast cancer and in bladder cancer show that a wide therapeutic window from a less potent payload, combined with drug leakage that results in a bystander effect in the tumour microenvironment, can improve outcomes.

"That deal made a lot of sense," says Alain Beck, senior director of Biologics CMC at the Centre d'Immunologie Pierre Fabre.

Drug discovery narratives and industry trends don't always follow the science, he cautions. And the longer-term value of ADCs remains to be established by empirical data in the clinic. "You have to be pragmatic,

Table 2 | **Top investigational mAb targets**

| Target | Investigational agent count[a] |
|---|---|
| PD1/PDL1 | 80[b] |
| CD3 | 71 |
| HER2 | 34 |
| CTLA4 | 25 |
| SARS-CoV-2 | 22 |
| 4-1BB | 19 |
| LAG3 | 19 |
| EGFR | 17 |
| CD20 | 15 |
| CD47 | 15 |

[a]Bispecific agents are included in these totals. [b]42 target PD1, 38 target PDL1. Sources: The Antibody Society, *Nature Reviews Drug Discovery*.

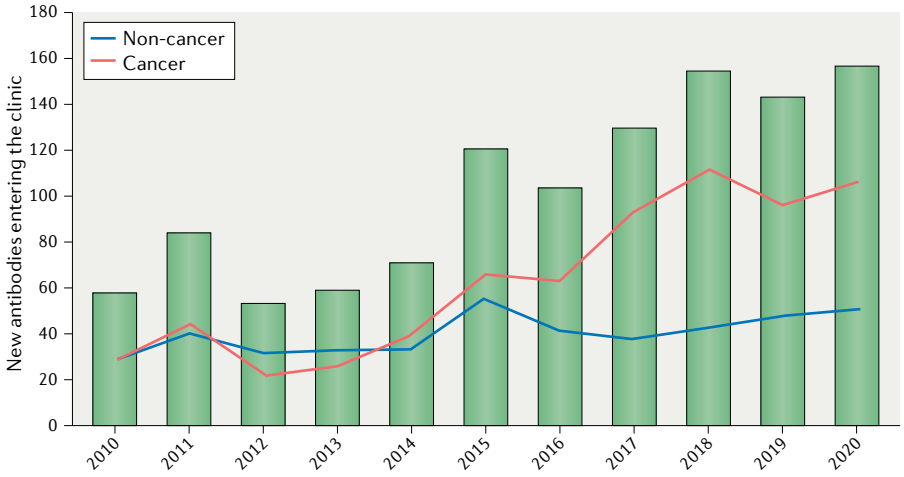


Fig. 3 | **New antibodies entering the clinic, by year.** New starts of cancer programmes have outpaced those of non-cancer programmes since 2014. Data include antibodies sponsored by commercial firms only, as of Q1 2021. Source: The Antibody Society.

and discuss these programmes with oncologists and physicians," says Beck.

A few companies are also pursuing non-cancer ADCs. AbbVie's phase II candidate ABBV-3373, for example, consists of an anti-TNF antibody fused to a steroid, for the treatment of rheumatoid arthritis. But Roche recently stopped clinical development of its RG-7861, a *Staphylococcus aureus*-targeted antibody fused to an antibiotic drug.

## Bispecific buy in

Bispecific agents have now taken on the role of the rising star of the antibody field. The FDA has approved only two bispecifics to date. But whereas 85 ADCs are currently in the clinic, nearly 160 bispecific and multispecific agents are in trials, show data from The Antibody Society. As such, bispecifics account for nearly 20% of the clinical antibody pipeline.

These candidates are a perfect fit for an industry fixated on immuno-oncology opportunities. While one arm binds cancer cells, the other recruits immune cells to where they are needed. The FDA's approval of its first bispecific — Amgen's blinatumomab for acute lymphoblastic leukaemia, in 2014 — provides a case in point. One arm binds CD19 to capture malignant B cells, while the other binds CD3 to recruit T cells. The result is targeted B cell depletion.

But bispecifics have yet to prove their ability in solid cancers. And CD3 — dubbed "the best supporting antigen" by Reichert because it is used in so many cancer bispecifics — carries considerable safety concerns. The term "cytokine release syndrome" was first used after researchers realized that muromonab-CD3 could trigger systemic inflammatory responses. And blinatumomab is still burdened with this potentially fatal toxicity profile.

Other cancer antigens, different immune cell targets and novel antibody technologies could help. "We are always asking what the next big thing is, and how we can overcome the limitations of existing therapies? I think that's exactly what bispecifics and multi-target therapeutics will enable us to do," says Skokos. Regeneron now counts bispecifics as a key pillar of their overall antibody strategy.

Already, it has four CD3-targeting bispecifics in the clinic. The other arms of these agents target BCMA (two agents), CD20 and MUC16. Whereas CD3 provides a first priming signal for T cells, Regeneron researchers also hope to harness co-stimulatory antigens to boost the power of the immune response further. In 2020, it advanced three CD28-targeting bispecifics into the clinic. The other arms of these target PSMA, for prostate cancer, MUC16, for ovarian cancer, and EGFR, for solid cancers.

By combining CD28-based bispecifics with other agents, including CD3-based bispecifics, Regeneron hopes to enhance activity further still.

"This is just the beginning," says Skokos. "If the early data look good, I believe this is going to be the next revolution in cancer immunotherapy."

Sanofi, another firm with bispecific ambitions, even has a trispecific in the clinic that binds both CD3 and CD28 on T cells, and CD38 on multiple myeloma cells.

But Beck remains to be convinced by bispecifics. The risks of overactivating the immune system are massive, he argues. And just as high hopes for checkpoint inhibitors beyond PD1/PDL1 and CTLA4 have yet to pan out, the bispecific buzz might also be a pipe dream.

Whereas bispecifics outnumber ADCs in the development pipeline, he anticipates that when it comes to approvals ADCs will keep beating bispecifics for at least another 5 years.

Bispecifics can also open up therapeutic opportunities in non-cancer indications. With the FDA's 2017 approval of Roche's bispecific emicizumab — which brings together Factor IXa and Factor X for the

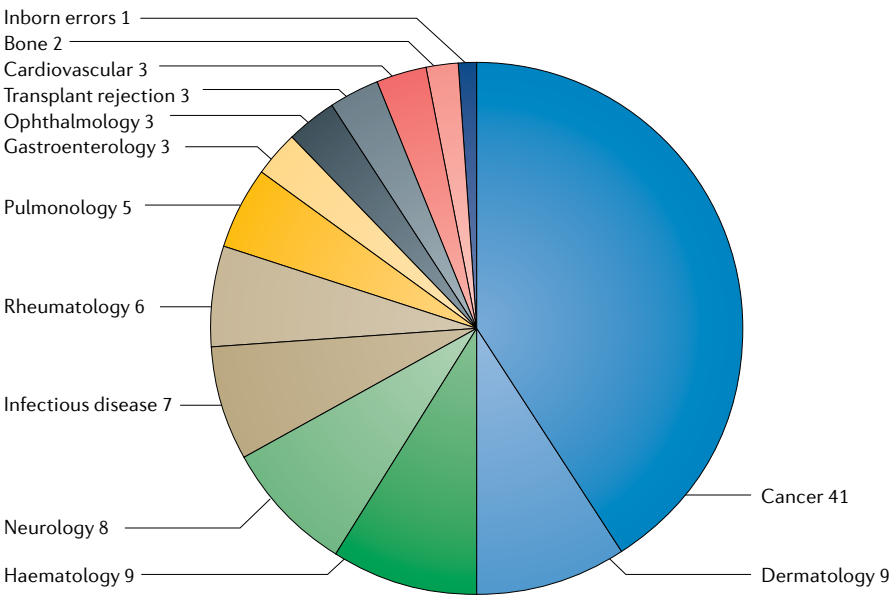


Fig. 4 | **The FDA's first 100 antibody approvals, by therapeutic area.** Therapeutic areas are based on the indication of the first approval only. Cancer includes haematological malignancies. Sources: The Antibody Society, Drugs@FDA, *Nature Reviews Drug Discovery*.

Table 3 | **Top mAbs, by 2019 sales**

| Antibody | Target | 2019 sales (US$ billion) |
|---|---|---|
| Adalimumab | TNF | 19.6 |
| Pembrolizumab | PD1 | 11.1 |
| Nivolumab | PD1 | 8.0 |
| Bevacizumab | VEGF | 7.1 |
| Rituximab | CD20 | 6.5 |
| Ustekinumab | IL-12/23 | 6.5 |
| Trastuzumab | HER2 | 6.1 |
| Infliximab | TNF | 5.3 |
| Denosumab | RANK-L | 5.0 |
| Eculizumab | C5 | 3.9 |
| Ranibizumab | VEGF | 3.9 |
| Ocrelizumab | CD20 | 3.7 |
| Secukinumab | IL-17A | 3.6 |
| Pertuzumab | HER2 | 3.6 |
| Golimumab | TNF | 3.4 |
| Omalizumab | IgE | 3.2 |
| Daratumumab | CD38 | 3.0 |
| Vedolizumab | α4β7 integrin | 2.5 |
| Dupilumab | IL-4Rα | 2.3 |
| Tocilizumab | IL-6R | 2.3 |

mAb, monoclonal antibody. Source: Cortellis.

treatment of haemophilia A — Roche showed how these agents can do more than just facilitate T cell recruitment.

Researchers are also exploring bispecific strategies as a means of smuggling antibodies into the brain, as well as into other hard-to-access organs. Roche's RG6102, for example, consists of an anti-amyloid antibody fused to a 'brain shuttle' antibody fragment that binds the transferrin receptor. When the transferrin receptor transports iron across the blood–brain barrier, it will take the biologic with it. Phase I data recently showed that RG6102 achieved an eightfold increase in antibody levels in the CNS compared with a canonical approach.

Roche plans to advance RG6102 into phase II trials shortly.

### Further frontiers

Smaller antibody structures including antigen-binding fragments (Fab) and domain antibodies could be the 'sleeper' format of the antibody modality. Although the second ever antibody approved by the FDA was Lilly's abciximab — a Fab that binds the αIIbβ3 integrin to prevent clotting in patients undergoing percutaneous coronary intervention — many drug developers have turned their backs on unaltered versions of these smaller formats. Not only do these structures tend to have a shorter half-life and poorer potency than full-length comparators, but they also have yet to find a biological niche in which their small size alone adds therapeutic value.

Genentech's ranibizumab, a VEGF-targeting Fab approved in 2006 for age-related macular degeneration, is the only non-canonical candidate to break into the top-20 antibody list by sales. But it seems to owe its success more to savvy development and commercialization than to underlying clinical advantages. Genentech's first-in-class VEGF-targeting bevacizumab and ranibizumab are both derived from the same parent mouse antibody. The Fab is one-third the molecular weight of its anti-cancer sibling, which in theory means that it might be able to better penetrate the retina. But clinical trials suggest that the two antibodies have equivalent activity.

But smaller biologics could yet take off, if they prove to offer new routes of antibody administration, better stability, new targets, improved immunogenicity or other benefits, say advocates. Frank Nestle, CSO at Sanofi, for instance has high hopes for nanobodies, a camelid-derived single-domain format that is a tenth the size of canonical antibodies.

Nestle helped engineer Sanofi's 2018 acquisition of Ablynx, a nanobody pioneer. In 2019, the FDA's approval of Sanofi and Ablynx's von Willebrand factor-targeting caplacizumab, for acquired thrombotic thrombocytopenic purpura, marked the first green light for a domain antibody.

More domain antibodies are on the way. "We're working very hard on this. You will hear a lot about this over the next few years,"

> Where's the niche? If you keep that in mind there are many possibilities

> The next 100 will be a lot faster than the first 100

says Nestle. Earlier this year, Sanofi partnered with i2O Therapeutics to work on oral delivery of nanobody candidates.

Although unaltered antibody fragments comprise only around 2% of the clinical pipeline, that undercounts the real interest in these formats, adds Reichert. Many drug developers use fragments to achieve other goals, including bispecificity, she points out. The first approved bispecific, Amgen's blinatumomab, consists of two single-chain Fv fragments fused together, for example.

Parren expects that smaller antibody formats will ultimately find broad success as bispecifics. At Lava Therapeutics, he is working with colleagues on bispecific domain-based candidates that will recruit γδ-T cells to cancer cells. "Where's the niche? If you keep that in mind there are many possibilities," he says.

Other antibody avenues also remain open.

Whereas many therapeutic antibodies block receptor–ligand interactions, agonist antibodies that mimic natural ligands to activate cell signalling have remained out of reach. Although GlaxoSmithKline recently floundered in a first ever phase III attempt with an agonist antibody, aiming to boost ICOS signalling, researchers are optimistic that they will eventually unlock this functionality. 4-1BB, number six on the list of top investigational antibody targets, is one such agonist opportunity.

Drug developers are also making inroads with antibody–protein fusion biologics. Antibodies fused with cytokines, receptor ligands, peptides and more could open up new possibilities. JR Pharmaceutical's JR-141, for example, consists of an enzyme replacement therapy fused to a transferrin receptor-binding antibody. This CNS-penetrant biologic was recently approved in Japan for mucopolysaccharidosis type II and is due to enter global phase III trials shortly.

One hundred approvals in, in other words, the field is only just getting started. "The next 100 will be a lot faster than the first 100," says Parren.