Face the unknown

Key bispecific antibody discoveries

1959 — Antibody architecture unraveled

1975 — Revolution of hybridoma technology

1983 — Quadroma technology enabled BsAb innovation

1986 — FDA approved first mAb therapy

1988 — ScFv transformed antibody engineering

1998 — BsAb pairing puzzle solved

2024 — Antibody diversity shapes the therapeutic landscape

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1959

Antibody architecture unraveled

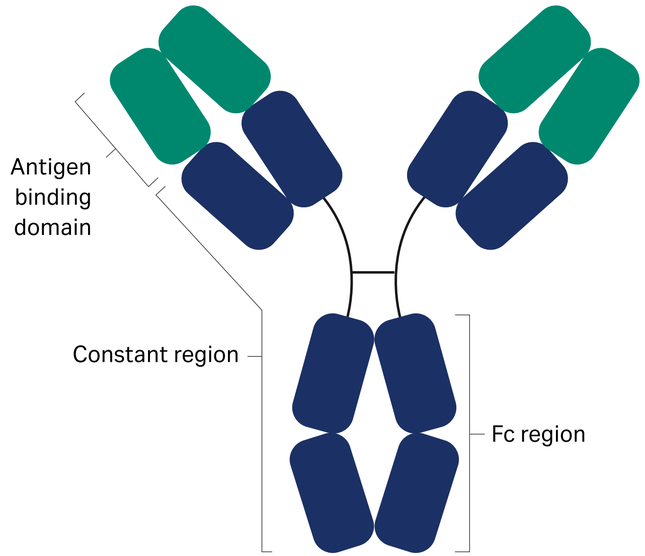
Antibody architecture unraveled

Until the late 1950s, our understanding of the structure and function of antibodies was extremely vague.

This changed in 1959 when American biologist Gerald Edelman and British biochemist Rodney Porter independently described the chemical structure of antibodies for the first time.

This groundbreaking discovery led to the two scientists being jointly awarded the Nobel Prize in Physiology and Medicine in 1972.

Reference



IgG (M, 150 000)

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Revolution of hybridoma technology

Even with the newfound understanding of antibody structure, scientists were still restricted by an inability to isolate and purify specific antibodies.

In 1975, Georges Köhler and César Milstein published a report in Nature describing the development of hybridoma technology.

This method, which supported the large-scale production of monoclonal antibodies (mAbs) directed against specific antigens for the first time, and paved the way for mAb commercialization.

Hybridoma technology had a profound impact on research and diagnostics, heralding a new era of mAb therapies.

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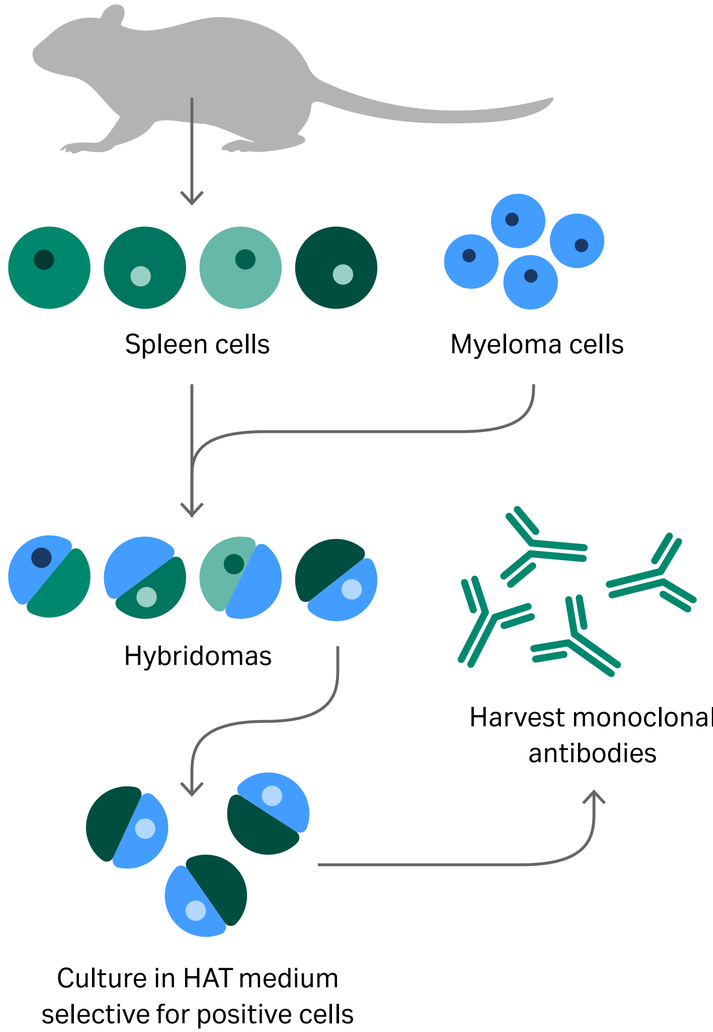

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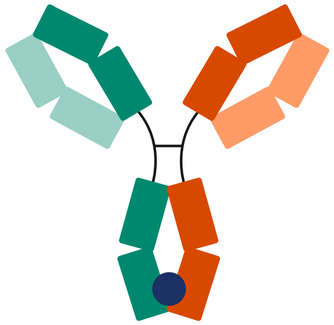
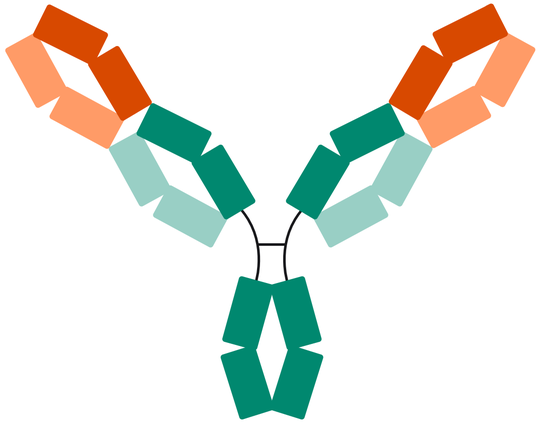
Quadroma technology enabled BsAb innovation

This revolutionary work was continued by Milstein, who pioneered the development of hybrid-hybridoma (quadroma) technology with his colleague Cuello. They published their findings in 1983.

The development of quadroma technology represented an early attempt to produce BsAbs. BsAbs are designed to bind two specific antigens or epitopes simultaneously to redirect immune cells, such as T cells, neutrophils, and macrophages, to tumor cells, resulting in tumor cell lysis.



"Knobs into Holes" approach



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FDA approved first mAb therapy

In 1986, the focus shifted back to mAbs as the FDA approved the first-ever mAb-based therapy, muromonab-CD3 (Orthoclone OKT3). OKT3 is a murine mAb therapy given to reduce acute rejection in patients undergoing organ transplants.

OKT3 had great potential, but induced immune responses in patients, leading to major adverse effects.

This setback spurred further research into techniques aimed at transforming rodent antibodies into structures more similar to human antibodies. The next antibody therapy would not be approved until eight years later, in 1994.

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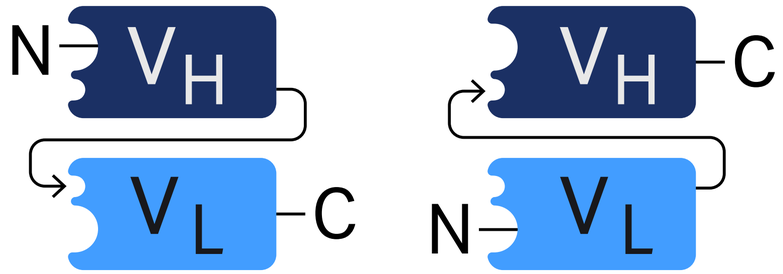
ScFv transformed antibody engineering

Alongside ongoing efforts to develop effective antibody-based therapies, research efforts continued to work towards development of novel antibody variants aimed at addressing the limitations of existing approaches.

In 1988, Huston and colleagues described the invention of the single-chain variable fragment (scFv). An scFv is a fusion protein of the variable regions of heavy and light immunoglobulin chains connected by a flexible linker.

The scFv retains the specificity of the original immunoglobulin while minimizing the challenges caused by the refolding of two-chain species, such as incorrect domain pairing and aggregation.



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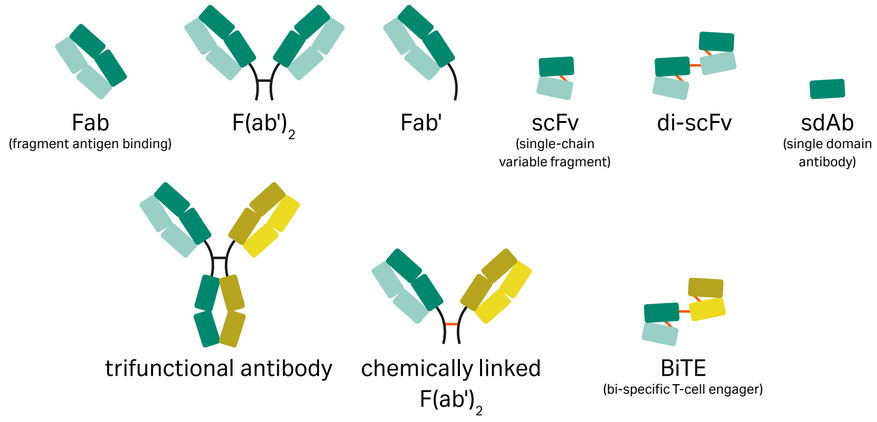
BsAb pairing puzzle solved

Building on earlier work, the 1990s provided further development of BsAb technology to address the difficulties scientists frequently faced surrounding expressing two different antibodies with the correct pairing.

In 1998, Margaret Merchant and team described the development of an efficient production pipeline for BsAbs, combining engineered disulfide bonds with previously identified “knobs-into-holes” mutations.

Overcoming hurdles in BsAb production represented a huge win, given the potential for these antibodies as therapeutic agents for cancer treatment.



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1998 — BsAb pairing puzzle solved

2024 — Antibody diversity shapes the therapeutic landscape

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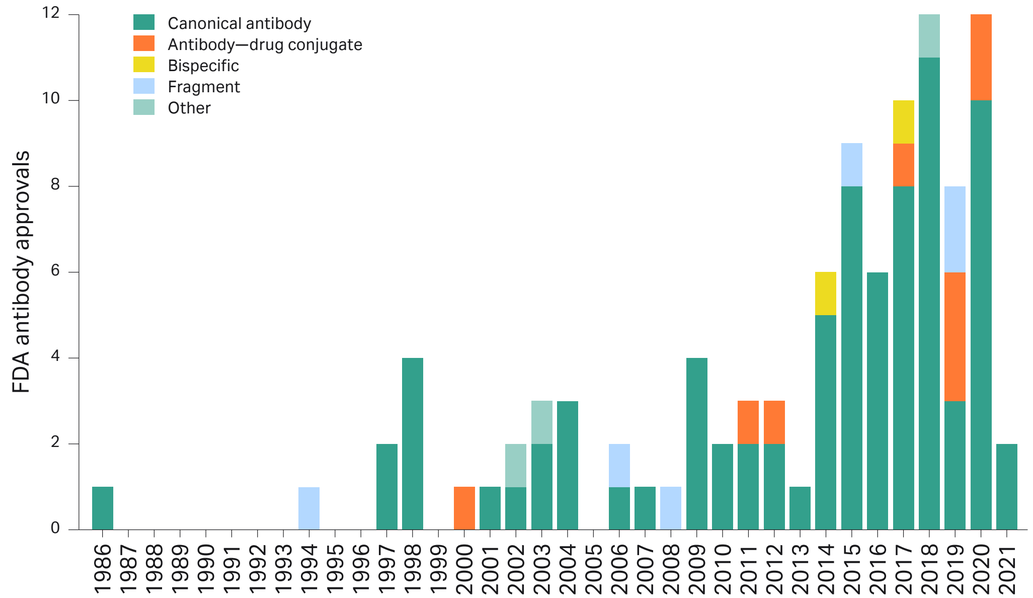
Antibody diversity shapes the therapeutic landscape

Together, these significant milestones and transformative discoveries in antibody research and development led us to where we are today.

Today, most approved antibodies on the market are full-length antibodies of the IgG1, IgG2, or IgG4 subclass.

Numerous alternative formats are available to address different clinical situations, including nine globally approved bispecific antibodies, with 180 more in preclinical trials and 50 in clinical trials.



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Antibody diversity shapes the therapeutic landscape

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Let’s face the challenges of drug discovery together

The development of BsAb-based therapies has had a considerable impact, especially given their broad applicability and superior therapeutic potential compared to mAbs.

To ensure high therapeutic efficacy and safety, researchers should design or select BsAb candidates that are easy to express and result in a high proportion of correctly assembled units with minimal aggregation. Moreover, BsAb candidates must meet formulation requirements for clinical use, which demand favorable solubility, high stability, and low viscosity.

Additionally, selecting a BsAb for clinical development requires a comprehensive assessment of functionality and target binding characteristics to ascertain a specific and balanced affinity for both targets, avoiding off-target binding.

Thankfully, designing optimal BsAbs has been made easier by recombinant DNA technology and advances in protein engineering. These technologies have evolved the design of BsAbs based on the heterologous combination of heavy and light chains.

Cytiva has over 300 years of experience with global innovations and discovery. You can benefit from our tools, knowledge, and support at every step of your BsAb therapy development process.

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