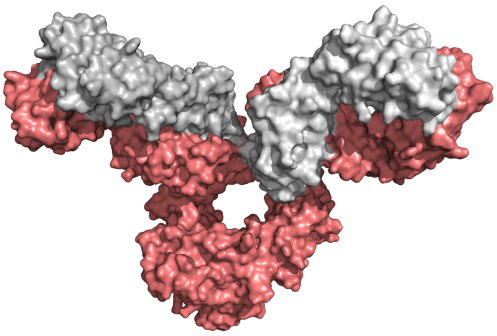
All about antibodies

Nature's protection

Antibodies are powerful, Y-shaped proteins that are key to immune system function. They help orchestrate the response of a variety of specialized proteins against foreign invaders in most vertebrates. The most common antibodies are immunoglobulins (IgGs), which are globular proteins that circulate in mammalian bloodstreams.

Antibodies are produced by white blood cells to identify and bind to targets, called antigens, which include foreign invaders such as viruses and bacteria. Though IgG antibodies are much smaller than a virus, they're essential to guiding white blood cells to find and destroy microbes and other invaders.



A computer model of an immunoglobulin. IPI image by Christopher Bahl

How scientists use antibodies in research

While the human immune system naturally makes antibodies to target foreign invaders, biologists have spent decades engineering ways to exploit their binding and homing abilities.

Scientists can use antibodies to illuminate the locations of proteins in living cells and tissues, identify mutations in a microbe's structure, track proteins in cells at various stages of a disease and more. Also capable of blocking protein functions, antibodies can uncover the biological impacts of diseases and, ultimately, inform therapeutic cures.

Some of the most common uses of antibodies in laboratories include:

- **Immunohistochemistry**, a technique that uses antibodies to detect proteins in a tissue sample
- **Western blotting**, a technique to identify a specific protein in a mix of others
- **Enzyme-linked immunosorbent assay**, a technique to detect and quantify biological molecules, including peptides, proteins and hormones.
- **Flow cytometry**, a popular way to analyze the chemical and physical properties of cells

Despite their promise, antibodies face major hurdles

Antibodies have helped basic scientists achieve new levels in their experiments thanks to decades of progress. But time has also revealed the limitations of contemporary antibody technologies.

Initially, scientists relied on **polyclonal antibodies**, naturally made by immune cells. Researchers produce polyclonals by injecting the protein they want to study into an animal — usually mice, rabbits or llamas — to induce its immune system to produce antibodies against that protein.

But with that method comes major hurdles. The animals produce a unique mix of antibodies against the injected protein, severely limiting specificity. When the animal dies, so does that collection of antibodies, making the reproducibility of results impossible from study to study over time.

A breakthrough came in 1975, when Georges Köhler and César Milstein, once a mentor to Institute for Protein Innovation (IPI) co-founder Timothy Springer, invented hybridoma technology, the first way to produce long-lasting antibodies. Researchers could immunize a mouse and extract a single antibody-producing cell, fuse it to a cancer cell and create a hybridoma, an immortal cell culture that churns out identical antibodies in perpetuity.

The finding earned them the Nobel Prize and spurred a new class of antibodies — **monoclonal antibodies** — capable of much higher specificity.

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But researchers, including Springer, learned that hybridomas change over time as they divide, resulting in a mix of antibodies that drifts away from the initial one. Also, hybridoma technology still requires the immunization of animals, raising a key technical challenge: Some proteins are so central to the functions of their systems that they've persisted against nearly 100 million years of evolution. Known as conserved proteins, they make for challenging targets in basic science because animal immune systems cannot recognize them as foreign and fail to generate antibodies. It's a major barrier for scientists studying complex human systems that are highly conserved among mammals, such as the brain and stem cells.

Moreover, many life science companies don't thoroughly validate their products, resulting in antibodies that don't recognize the targets they're intended to or bind to other antigens with similar structures, called cross-reaction. This dearth of validated antibodies helped spur what's known as science's reproducibility crisis, a trend recognized around 2010 in which key studies — many using flawed tools — can't be verified by other researchers.

Let our proteins power your next discovery.

Institute for Protein Innovation

IPI aims to revolutionize biology with new technology and open science

IPI scientists specialize in generating synthetic, recombinant antibodies, which are made in organisms such as yeast using synthetic DNA. IPI scientists engineer yeast cells to make antibody fragments, capable of binding target proteins, and display them on their surfaces. Researchers create “libraries” of billions of yeast, each making its own antibody fragment. The diversity mimics what happens in the human body, which houses billions of cells, each carrying a potential antibody displayed on its surface.

In a well-tuned sorting process, IPI scientists tap the libraries to find the best yeast binders for a target of interest. Those binders become candidates for further testing, characterization and ultimate packaging into recombinant antibodies.

Because the technology is reliant on knowledge of the DNA sequence of the antibody binding fragment, synthetic antibody approaches ensure reproducibility. The method is among the best ways to generate reproducible antibodies for highly conserved targets. Protein scientists can also use advanced engineering techniques to generate antibodies with specific abilities beyond binding, such as function blocking or locking protein shapes for researchers to study.

Because IPI is a nonprofit, sustained in part by philanthropy, we’re poised to make antibodies widely available to biological researchers and share our data. This commitment reflects IPI’s contribution to the open science movement, which aims to enable accessibility to research data, samples, software and tools.

Nicholas Hollmer, a research associate on IPI's Antibody Discovery team. IPI photo by Pat Piasecki

Mina Abdollahi, left, and Filmawit Belay, right, of IPI's Antibody Production team. IPI photo by Pat Piasecki

Shaotong Zhu, principal scientist. IPI photo by Pat Piasecki.