REDDIT:

I've been trying to learn how new antibodies are made, and from what it sounds like, B-cells do random gene recombinations so each one has different receptors on the outside. Then, an antigen from a new infection is shown to B-cells until it binds to one, and that cell starts producing the antibodies its unique DNA codes for.

That can't really be what happens, right? There are a hundred billion variations of receptor, so does a new antigen really have to be presented to billions of B-cells before a match is found? That seems impossible.

Response:

When the stem cells that eventually become B cells are developing, they undergo a process known as V(D)J recombination. Basically, this allows developing B cells to rapidly mutate their antibody-encoding genes so that they come in many different shapes/specificities. Note that each B cell only expresses one “shape” of antibody.

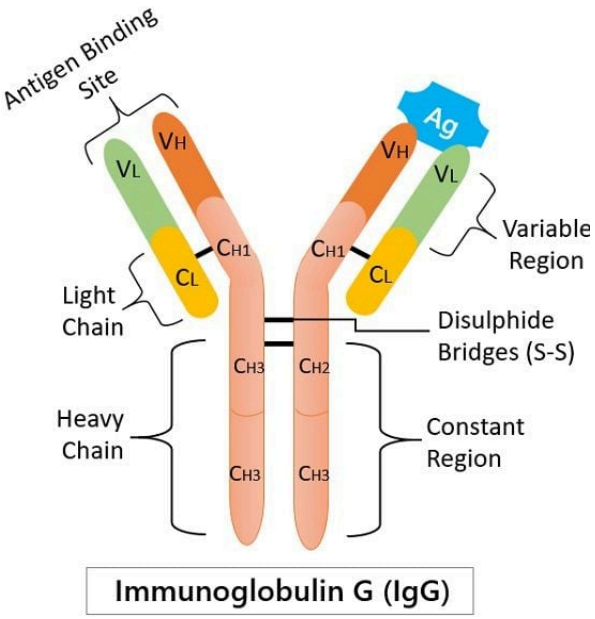
Before they’re activated by a pathogen, B cells express their antibodies on their surface (sometimes known as B cell receptors). When these surface-bound antibodies come into contact with pathogenic material that fits their specific shape, the B cell can become activated. Activated B cells then begin secreting antibodies.

It may also interest you to know that activated B cells in your lymph nodes and spleen can also undergo a process whereby they’re “trained” to produce antibodies that are even more specific for the pathogenic material. This training is also known as affinity maturation which consists of two major steps: somatic hypermutation and class switching. Basically, the activated B cell rapidly begins to proliferate. As it proliferates, the new clones rapidly accumulate mutations that further change their antibody shape. B cells with mutations that generate antibodies with lower specificity are killed off. Those that have higher specificity eventually go out into the body and fight the infection. Or they undergo further rounds of affinity maturation.

Links included in case you wanted the nitty gritty deets. Lmk if you have any questions

Edit: also worth mentioning, a specific B cell antibody may have affinity for multiple antigens. I suppose an analogy might be a catchers mit in baseball. It’s designed to catch a ball (high affinity) but you could probably catch a Rubik’s cube if you tried (low affinity).

https://www.reddit.com/r/askscience/comments/ne0290/do_bcells_really_generate_randomly_shaped/



Immunoglobulin G (IgG)

Compare/Contrast innate and adaptive immunity

Feature	Innate	Adaptive
Speed	Minutes–hours	Days
Specificity	Pattern-based	Antigen-specific
Memory	No	Yes
Key cells	Macrophages, neutrophils	B cells, T cells

Common student confusion points (worth emphasizing)

1. **Humoral ≠ innate**
   Antibodies are *adaptive*, not innate.
2. **Cellular ≠ innate**
   “Cell-mediated” here refers to **T cells**, not macrophages.
3. **Adaptive = humoral + cellular**
   These are subdivisions, not alternatives.

The Classroom Mystery: Two patients walk into your clinic. Both are completely healthy and asymptomatic, but both show positive IgG antibody tests for a specific virus.

- **Patient 1** has a wide variety of IgG antibodies that bind to the virus's outer spike *and* its internal core proteins.
- **Patient 2** *only* has IgG antibodies that bind to the outer spike protein. They have zero antibodies against the internal core.

Work with your table team to provide an evidence based explanation.

Where antibodies exist in nature

Only in jawed vertebrates (Gnathostomes)

True antibodies (immunoglobulins with Ig domains, V(D)J recombination, and class switching) are found in:

- Fish (cartilaginous and bony)
- Amphibians
- Reptiles
- Birds
- Mammals

They **do not exist** in:

- Invertebrates (insects, mollusks, worms)
- Plants
- Fungi
- Bacteria or archaea

So antibodies are **not a universal immune strategy**.

Evolutionary origin: step by step

1. Ig domains came first

- Ig-like domains are ancient
- Found throughout metazoans in:
    - Cell adhesion molecules
    - Neural recognition proteins
- So the *fold* is old; immunity is a later reuse

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2. Somatic recombination was the breakthrough

The key innovation was **V(D)J recombination**.

- Required the evolution of **RAG1 and RAG2**
- RAG proteins likely originated from a **transposase**
- A transposon inserted into an ancestral Ig-domain gene
- This allowed **cut-and-paste assembly** of variable regions

This event occurred ~**500 million years ago**, just before the emergence of jawed vertebrates.

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3. Clonal selection emerges

Once rearrangement existed:

- Each lymphocyte expressed a unique receptor
- Antigen-driven expansion became possible
- Immunological memory followed naturally

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4. Diversification of antibody classes

Later innovations added:

- Class switching (IgM → IgG, IgA, IgE)
- Affinity maturation via somatic hypermutation

These refinements increased **effector flexibility**, not recognition per se.

What about jawless vertebrates? (important exception)

Lampreys and hagfish **do not have antibodies**, but they *do* have adaptive immunity.

Variable lymphocyte receptors (VLRs)

- Based on **leucine-rich repeats (LRRs)**
- Assembled by gene conversion, not V(D)J
- Functionally analogous to antibodies

This shows:

> Adaptive immunity evolved **at least twice** using different molecular scaffolds.

Example	Heavy Chain amino acids	Light Chain amino acids
Complementary Binding Region (CDR)	**V3, J1, D3**	**V3, J1**
1	Phe, Leu	Phe, Glu
2	Leu, Val	Ala, Asp
3	Glu, Leu	Glu, Ala

	Heavy Chain amino acids	Light Chain amino acids
Complementary Binding Region (CDR)		
1		
2		
3		