The Antibody Society's 2022 Science Writing Competition

Student winner

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Immunity in a Deck of Cards

Paris 1884

The year is 1884, a mother and her daughter walk on the grass near the water's edge. The mother caring a red parasol and wearing a matching blouse; her daughter pulls tight on her skirt to keep close. The two are walking past a man relaxing in the shade smoking a pipe, his dog behind him sniffing the grass, unaware of another dog coming to greet him. The mother and daughter look out at the water. Many people are out on river Seine. Little dinghies, and rowboats glide across the

water making their way around the little island on a Paris Sunday.

This scene is one you have almost certainly seen before. It is one of the most remarkable paintings of the nineteenth century. *A Sunday on La Grande Jatte—1884*, is now considered Georges Seurat's greatest work. The French impressionist became famous for his technique of meticulously painting tiny ball shaped points of contrasting pure color to create huge compositions. The effect is spectacular in person. The tiny dabs of color placed with scientific precision appear as dense confetti when viewed up close. From afar, the brush strokes are too small to be distinguished and only then the entire work comes into view.

Figure 1: (Left) A Sunday on La Grande Jatte — 1884 by Georges Seurat. (Right Top) Close-up views of the child and man smoking a pipe. (Right Bottom) Additional close-ups of the multi-color pointillism brushstrokes in the child and man.

The cells of your immune system are akin to Seurat's points of color on canvas; innumerous, tiny, and unique specs of color. As immunologists we are often hyper focused on the

close-up details of the cells in our immune system, or dots on the canvas. However, to understand not just the mechanisms of immunology but an entire system it-self, we need to take a few steps back to see the greater picture and for that scene of a Paris Sunday to come back into focus.

Infection vs. Diversity

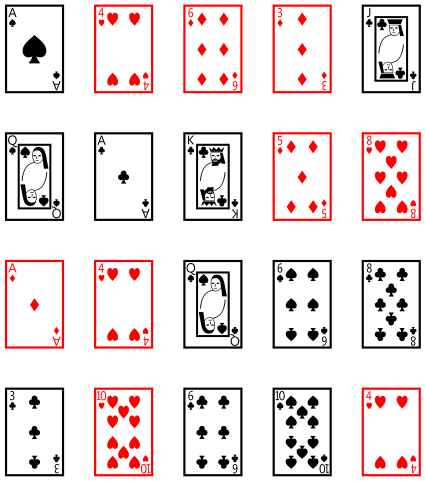
The coronavirus pandemic has convinced many of us that the immune system is the most important thing which we don't know enough about. How exactly does our body protect us against germs intent on making our cozy warm body their new home? Imagine you cut yourself while doing yardwork. A virus makes its way into your body and starts infecting other cells and kicks your immune response into action.

By now, you have probably heard about antibodies. These are made from a specialized white blood cell called 'B cells'. Our immune cells are blind. B cells crawl around in the dark and use antibodies to 'feel' around them to navigate their world. When an antibody *sees* the right protein, it sticks to it. Thankfully, this specific antibody was able to recognize one of the proteins on the invading virus and latch onto the it. This binding of the antibody prevented the virus from being able to infect other cells.

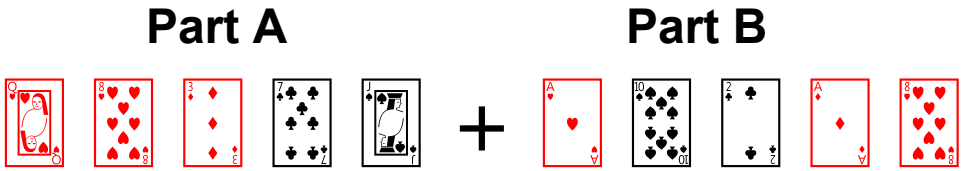
Antibodies can bind to almost anything and each individual antibody binds to extremely specific targets. It's easy to gloss over this simple fact and not give it the consideration and wonder it deserves. This is truly amazing if we really consider what that means. Your genome has approximately 20,000 genes[1,2]. In general, each of these genes encodes for a single protein. How can one protein be able to attach itself to anything? Imagine how many molecular structures there are in the world. To give you an idea, there are an estimated one trillion species of microbes on Earth, and 99.999% of them have yet to be discovered[3]. Let's imagine there are 1000 genes in each of these microbes, each of which encodes for a unique molecular structure. Amazingly, this infinity of structures can all be seen by antibodies. Even microbes which might exist in the future, but do not even exist yet can be seen by antibodies. How can the body adapt to create specific defenses for all these molecular structures, and millions more which don't exist yet? The perplexing reality is that the immune system comes pre-installed at birth with at least one cell inside you which has the ability recognize any kind of possible threat in the universe. Right now, those cells are still inside you, waiting for the chance to be activated by their target 'antigen' (a piece of the enemy).

Dealers Choice

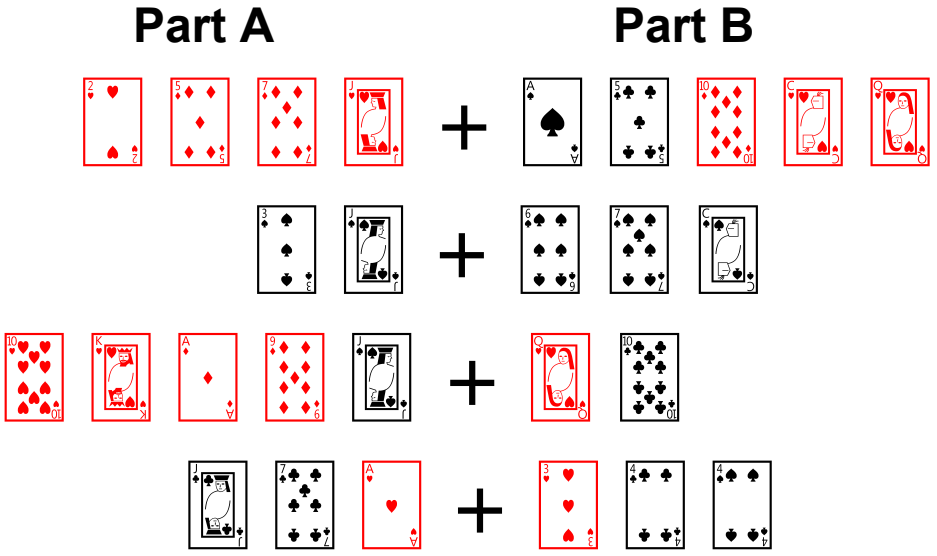
We would need an infinite number of genes to encode for unique antibodies if there was a one-antibody one-gene model. However, over millions of years our immune system has devised an ingenious way to minimize the number of genes which code for antibodies to solve this problem, a cheat code. The trick is the immune system developed a way use small fragments of genes to be mixed and matched to create a magnificent diversity of unique receptors which recognize the antigens of the world. Let's consider these gene fragments as individual cards from a standard playing deck. The deck has four suites: Diamonds (♦), Clubs (♣), Hearts (♥), and Spades (♠). Each suite has 9 numeral cards (2-10), 3 face cards (Jack, Queen, King) and 1 Ace card. Thus, the entire deck has 52 cards total. Say you draw a 5-card hand for a game of poker. You draw the following hands as you start to play:



And so on. All and all, from 52 cards and picking 5-card hands at a time a total of 2,598,960 distinct poker hands can be drawn. Now the receptors of the immune system do this twice, as their antigen receptors are broken up into a 'Part A' and a 'Part B'. We can continue our card analogy by picking up a second deck of 52 cards for our 'part B' antigen receptors. With this deck, we deal ourselves a second random 5-card hand:



With 10 cards we are now into many tens of millions of distinct poker hands. However, we can get even more variety by randomly adding or removing the number of cards we draw in each hand. For example, some of the final hands might be:



By now we have many billions of unique two hand card combinations. In the immune system, this reshuffling process occurs in much the same way as our card analogy. The resulting rearrangement

of gene fragments produces antigen receptors imbued with new and specific sensitivity to a target antigen. This process, known as V(D)J recombination, is among the most complicated aspects of all immunology. In fact, this discovery that antibodies are not governed by a rule of one gene → one protein was so significant it was awarded the 1987 Nobel Prize in Medicine[4]. The implication of this discovery lives on today as V(D)J recombination and immune receptor diversity is also fundamental to our understanding of how we can design effective vaccines, cancer killing therapies and survive the day-to-day attempts by germs to invade our bodies.

V(D)J recombination takes place in the B cells to make antibodies which 'see' antigens on the surface of germs molecular structures. Another kind of cell, called a 'T cell', recombines to make a molecule, which acts as a counterpart to antibodies, and sees antigens inside these molecular structures . Each of these individual B and T cells recombines to have a single "unique two hand gene (card) combination".

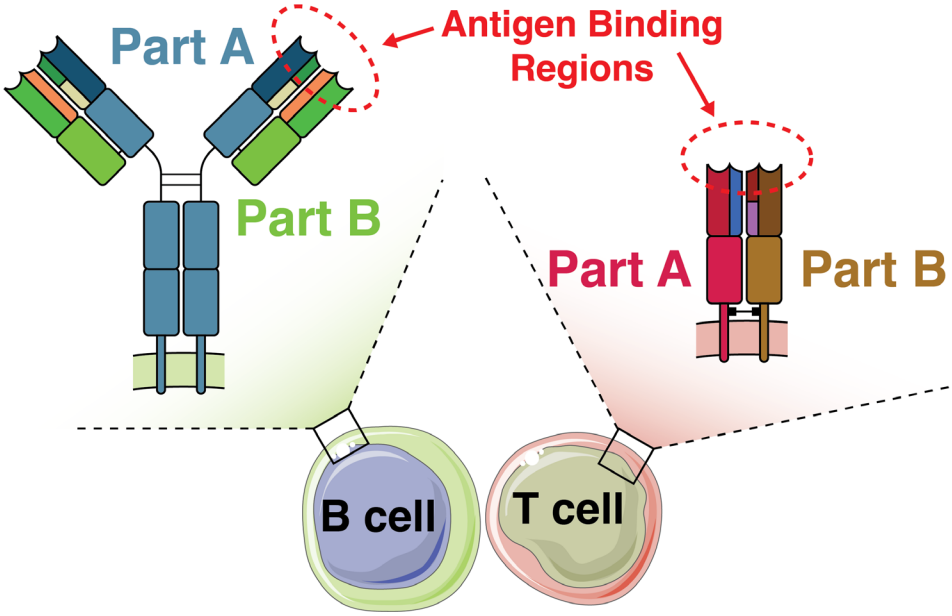


Figure 2: Cartoon of B cell antigen receptors (antibodies) and their counterparts on T cells (T cell receptors). Highlighted are the 'Part A' and 'Part B' segments which rearrange via V(D)J recombination to give these molecular structures diversity and the ability to detect different antigens on viruses, bacteria etc. Antibodies detect surface antigens while T cell receptors detect internally 'hidden' antigens.

Consider the Whole Deck

The collection of all the unique combinations of B and T cells in our bodies is called a repertoire. This catalogue of B and T cells differs between person to person, so much so that identical twins do not share the same repertoires[5]. Despite this diversity, these repertoires tend to narrow in on common targets which expose identifiable patterns after infections and numerous diseases settings[6–10]. Some of these patterns of immune repertoires hold the secrets to understanding why some people get autoimmune diseases or infections meanwhile others are resistant to HIV or cancers. One of the goals of examining these repertoires is to use this information as diagnostic and predictive tools. For example, immune repertoires may help make early diagnoses to auto-immune diseases or cancer. Alternatively immune repertoires may be used in predicting which people are going to be more susceptible to getting sick from infectious diseases or respond better to vaccines. Right now, the picture of immune repertoires is fuzzy. Scientists are

just now beginning to develop the computational and biotechnology tools to view the canvas of the immune repertoire in its entirety[11,12]. However, patches of the picture are beginning to come into clear focus; giving us a glimpse of what future medicine will be able to do.

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