ILD Collaborative

A Patient-Physician Collaborative for the Understanding, Management, and Treatment of Interstitial Lung Diseases

Immunogenetic Diversity
On Compatibility Genes, and Interferon-Stimulated Genes

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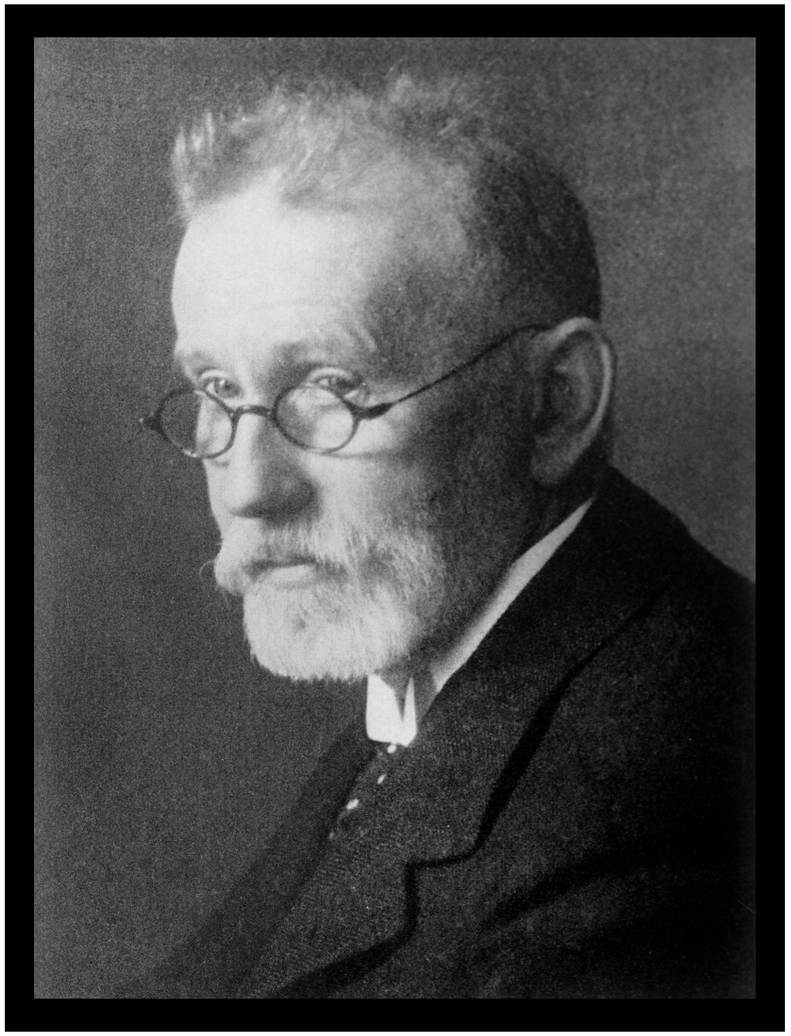
“Magic Bullets” in the Plasma



Experimentelle Untersuchungen über Immunität.

Ehrlich P.

Dtsch. med. Wochenschr. 1891;17(1218)

“Magic Bullets” in the Plasma

Paul Ehrlich (1854-1915): Early in his career Ehrlich began to develop a chemical structure theory to explain the immune response. He saw toxins and antitoxins as chemical substances at a time when little was known about their exact nature.

Ehrlich supposed that living cells have side chains—a shorter chain or group of atoms attached to a principal chain in a molecule. These side chains can link with particular toxins.

“Magic Bullets” in the Plasma

According to Ehrlich, a cell under threat from foreign bodies grows more side chains, more than are necessary to lock in foreign bodies in its immediate vicinity.

These ‘extra’ side chains break off to become antibodies and circulate throughout the body. It was these antibodies, in search of toxins, that Ehrlich first described as magic bullets (Zauberkugeln).

“Magic Bullets” in the Plasma

In his paper, Ehrlich hypothesized that if two cells give rise to two different antibodies, then they themselves must be different.

We now know that each B cell makes one type of antibody.

Experimentelle Untersuchungen über Immunität.
Ehrlich P.
Dtsch. med. Wochenschr. 1891;17(1218)

Clonal Selection Theory

The Mystery of Antibodies

Antibodies, discovered in the 1890s, are soluble proteins that stick to and can neutralize all kinds of germs and other potentially dangerous molecules.

How could antibodies attack so many molecules, yet not trigger an attack to the body's own cells and tissues?

Antibodies attack a limitless number of 'non-self' molecules, but normally do not mount an attack on 'self' cells and tissues.

Clonal Selection Theory

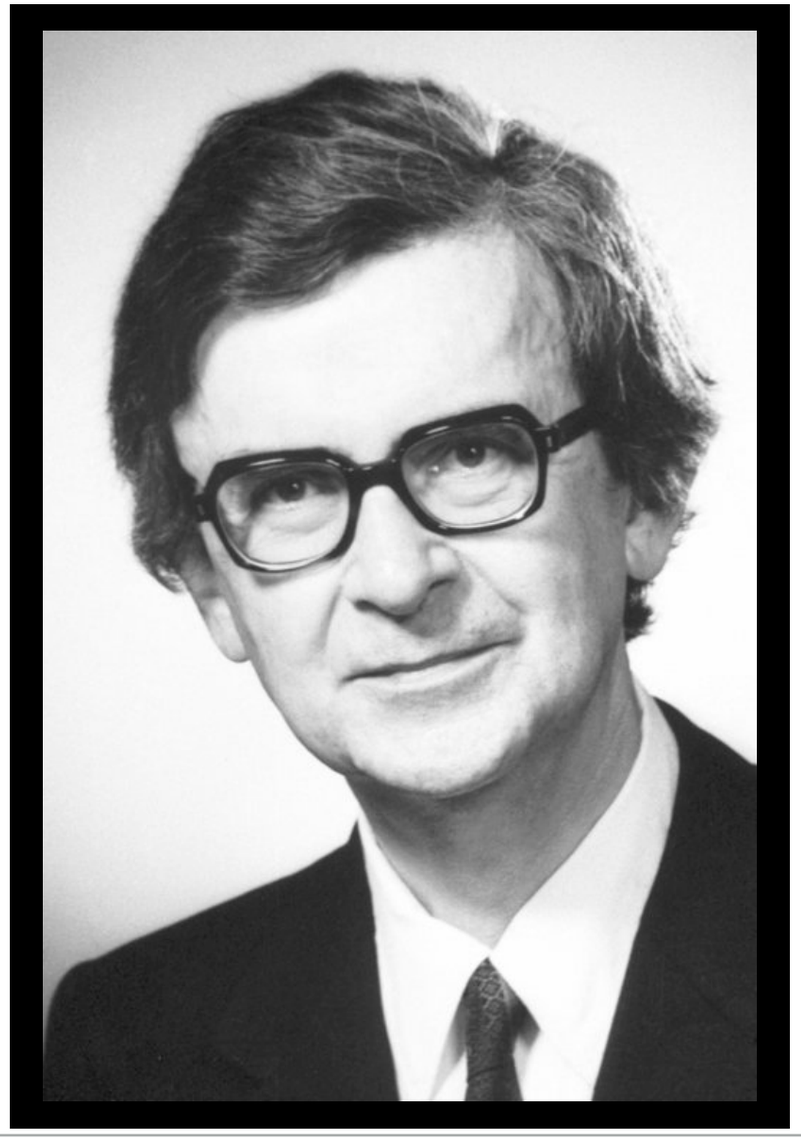
The Mystery of Antibodies

Linus Pauling's 'instructional theory' (1940): There is one template antibody that is 'instructed' by any foreign molecule it encounters to fold around it.

Problem (among others): Why would antibodies only fold around foreign/non-self molecules?

Niels Jerne (1955): All sort of differently shaped antibodies that bind to foreign shapes pre-exit and circulate in the blood before any germ has been seen.

Clonal Selection Theory



The natural-selection theory of antibody formation.

Jerne NK.

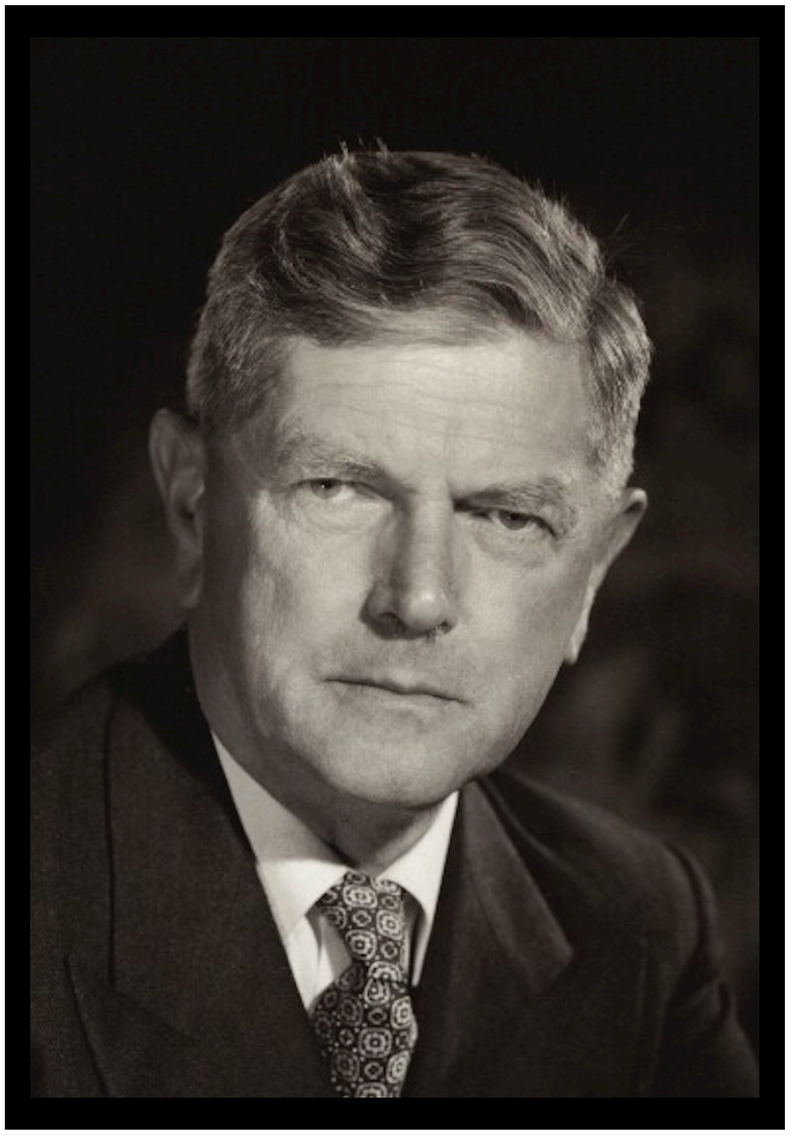
Proc Natl Acad Sci U S A. 1955 Nov 15;41(11):849-57.

Clonal Selection Theory

F. Macfarlane Burnet (1957): There are antibody-secreting cells, each of which makes one particular antibody. When the cell encounters a foreign molecule that its antibody can attach to, it multiplies, and makes lots of clones of the initial cell.The antibodies now secreted in bulk can efficiently neutralize the germ or dangerous foreign molecule.

For Burnet, this was Darwinian selection applied to the immune cells: germ fighting cells are activated to multiply and become the greater fraction of the population of antibody-secreting cells.

Clonal Selection Theory



A modification of Jerne's theory of antibody production using the concept of clonal selection.

Burnet FM.

Aust. J. Sci. 1957; 20(3):67-69.

Clonal Selection Theory

Several subsequent discoveries contributed to the affirmation of the clonal selection theory.

A series of experiments by Gustav Nossal showed that a single cell was capable of neutralizing one type of bacteria. So a single cell must just make one shape of antibody.

Antibody production by single cells.
Nossal GJ, Lederberg J.
Nature. 1958 May 17;181(4620):1419-20.

Clonal Selection Theory

At the time, it has been worked out that a single gene encodes the instruction to make a single protein.

It is estimated that there are 10-100 billon shapes of antibodies in the human immune system, far outstripping the number of genes we have (23,000). Thus it is impossible that each variation of antibody shape could be encoded by a gene.

How could an antibody-secreting cell make a differently shaped antibody?

Clonal Selection Theory

In 1987, Susumu Tonegawa won the Nobel Prize in Physiology of Medicine “for his discovery of the genetic principle for generation of antibody diversity.”

In experiments Susumu did in the mid 1970s, he discovered that antibody genes come in bits that join together in a myriad ways. While developing in the bone marrow, antibody-secreting cells, namely B cells, shuffle these genes so that each B cell ends up being able to make one antibody shape.

Clonal Selection Theory

The other type of immune cells in humans that shuffle their genes in this special way are T cells.

Each individual B or T cell reacts to a particular shape of molecule. Initially all kinds of B and T cell are produced, and could react to the body's cells and tissues.

A wonder of the immune system is that there are elaborate processes by which B and T cells that would react to the body's own cells and tissues (self) are eliminated.

Clonal Selection Theory

How does the human body discriminate self from non-self?

Burnet realized that the problem of how the body recognizes disease is part and parcel of how the body knows its own cells and tissues.

Acquired Tolerance

Self vs Non-Self: The Transplantation Problem

In 1945, Ray Owen published the observation that blood of non-identical cattle twins contained cells in common.

In the context of transplantation, this meant that blood cells can be transferred between non-identical cattle twins.

This showed that it is possible for cells from one animal to exist in another without any immune reaction occurring.

Acquired Tolerance

Self vs Non-Self: The Transplantation Problem

In 1949, building on Owen's discovery, Burnet speculated that the twins' tolerance for each other must have developed by the caves to the other's cells when still fetuses or in early childhood.

Burnet went on to hypothesize that our immune system must also learn to recognize the body's own cells and tissues in early development.

Burnet had no proof of this hypothesis, and remarked that "it remains to be seen whether this concept is of value."

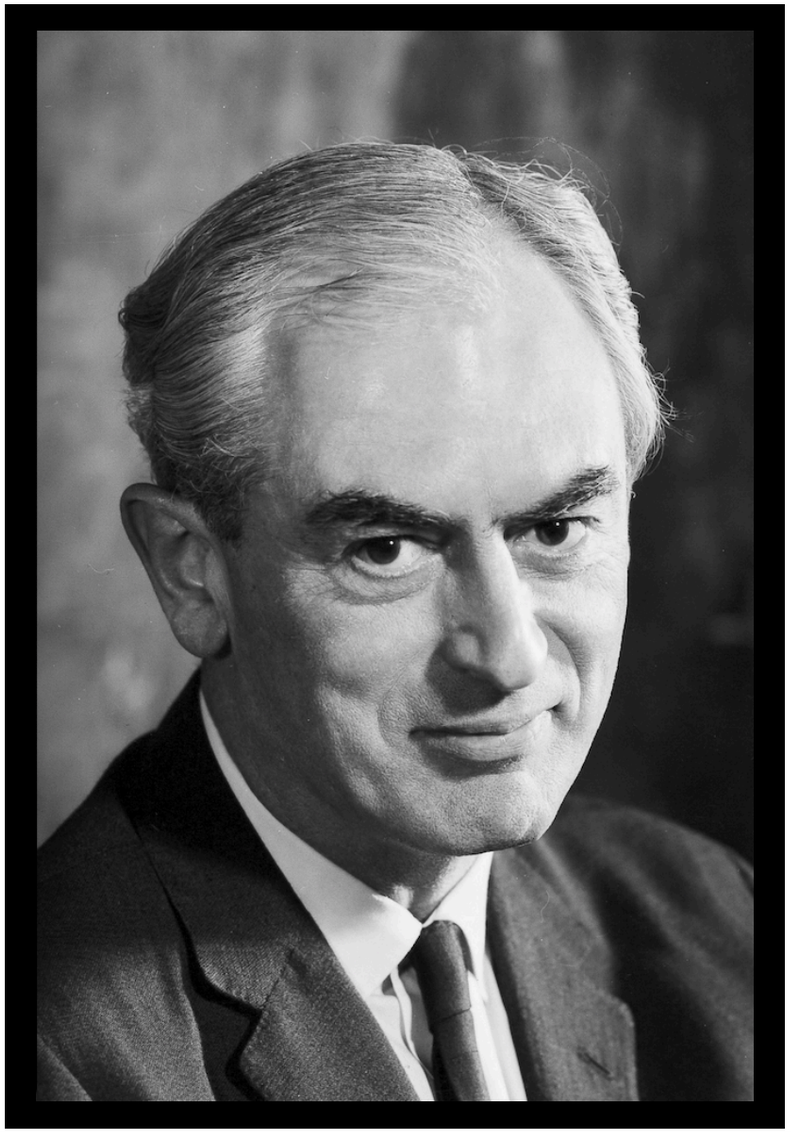
Acquired Tolerance

Self vs Non-Self: The Transplantation Problem

In the late 1940s, unaware of Owen's research, Peter Medawar, who has been studying graft rejection in humans, found out that cattle twins always accepted grafts from each other, no matter whether they were identical twins or not.

Medawar learned of Owen's 1945 observation when he read Burnet's 1949 paper. Owen's observation became the foundation for an ingenious set of experiments Medawar conducted that led to his seminal publication in 1953.

Acquired Tolerance



Actively acquired tolerance of foreign cells.

Billingham RE, Brent L, Medawar PB.

Nature. 1953 Oct 3;172(4379):603-6

Acquired Tolerance

Self vs Non-Self: The Transplantation Problem

Medawar and his team injected cells from one inbred mouse strain directly into unborn fetal mice of another, non-identical strain. After birth, when tested as adults, the injected mice were able to accept skin from the unrelated mouse strain whose cells had been injected.

This was a startling, groundbreaking finding. The mice has become tolerant to skin grafts from unrelated mice they had been exposed to when fetuses. Medawar and his team then went to verify that the process was also true for other species.

Acquired Tolerance

Self vs Non-Self: The Transplantation Problem

The transplantation problem has been solved! But in laboratory conditions, and in animals rather than humans. It would be impractical to inject cells into a human fetus.

Nonetheless, Medawar’s experiments showed that it is possible to breach the natural barrier for transplantation between unrelated animals.

Acquired Tolerance

Self vs Non-Self: The Transplantation Problem

Humans can only accept skin grafted from elsewhere on their own bodies. Skin taken from the bodies of others, even relatives, was rejected.

Up until Medawar's time, most surgeons thought that, if they could perform a technically perfect graft, the transplantation would work.

Medawar showed that this was wrong: there was the fundamental barrier of compatibility to be overcome in order for skin grafts between genetically different people to work.

Acquired Tolerance

Transplanted cells and tissues are recognized and rejected as non-self by the immune system.

What molecular substance gives each of us our individuality and how could our bodies distinguish it?

Through the work of another transplantation scientist, Peter Gorer, Medawar and his team knew that a genetic component was important in controlling transplant compatibility.

Acquired Tolerance

Burnet and Medawar won the 1960 Nobel Prize in Physiology or Medicine *“for the discovery of acquired immunological tolerance.”*

Jerne won the 1984 Nobel Prize in Physiology or Medicine *“for theories concerning the specificity in development and control of the immune system and the discovery of the principle for production of monoclonal antibodies.”*

Genetic Diversity of the Immune System

Today genetic matching and the use of immune-suppressive drugs make tissue and organ transplantation a life-saving reality.

What exactly is it that needs to be matched between people?

What are the big things that vary in cells and tissues from different people — things that the immune system is especially reactive to?

Genetic Diversity of the Immune System

Major Histocompatibility Complex (MHC)

1% of the human genome (23,000 genes) varies from person to person. MHC vary the most from person to person and have nothing to do with our appearance. These genes, when matched between donors and recipients, help provide the best chance of success in many types of organ transplantation.

But these handful of genes couldn’t exist just to make transplantation difficult.

What do these genes really do?

Genetic Diversity of the Immune System

Human Leukocyte Antigen (HLA)

These genes exist in other species, and in humans they are called the *human leukocyte antigen (HLA)* genes. They come in three classes, I, II and III. We each have six different class I HLA genes: 2 As, 2 Bs, and 2Cs (three from each parent). There are lots of known versions (alleles) of each gene: 1243, 1737 and 884 versions of the A, B and C genes respectively.

Why are there so many versions, and thus combinations, of the MHC/HLA genes leading to genetic immune variability between people?

Genetic Diversity of the Immune System

Non-Self is ‘Altered Self’

Until the mid 1970s most scientist believed that an immune cell would recognize a virus infection directly, without any restriction or influence from the type of cell infected.

Inspired by studies showing that mouse strains differed in their susceptibility to disease, Peter Doherty and Rolf Zinkernagel set out to compare the ability of immune cells from one mouse strain to kill virus-infected cells taken from other strains.

Genetic Diversity of the Immune System

Non-Self is ‘Altered Self’

In a series of ingenious experiments Doherty and Zinkernagel showed that cytotoxic T cells activated by a virus in one mouse strain where only able to detect the cells that had the same virus in another mouse strain which had the same class I major histocompatibility genes.

A biological role for the major histocompatibility antigens.
Doherty PC, Zinkernagel RM.
Lancet. 1975 Jun 28;1(7922):1406-9.

Genetic Diversity of the Immune System

Non-Self is ‘Altered Self’

The implication was that genes for transplant compatibility also control the immune response against a virus!

Over twenty five years earlier, in 1949, Burnet had articulated the idea that the immune system works by telling apart self from non-self.

Doherty and Zinkernagel suggested that immune system worked through recognition of ‘altered self’.

Genetic Diversity of the Immune System

Non-Self is ‘Altered Self’

A gene is essentially an instruction that cells use to make a particular protein.

A body’s MHC proteins, Doherty and Zinkernagel proposed, were ‘altered’ by the presence of a virus, and the body’s immune system could then identify disease as ‘altered self’.

They went further to offer an explanation of why there is such great diversity in our HLA genes: it would be harder for a virus to evade our immune systems if the process of detection varied.

Genetic Diversity of the Immune System

Non-Self is ‘Altered Self’

Put differently, we might have evolved diversity in HLA genes so that we are stronger at fighting off viruses — *as a population.*

The idea proved very insightful, specially because it wasn’t clear to anyone how the MHC/HLA protein could really be ‘altered’ by the presence of a virus.

T Cell Receptor

Following Doherty and Zinkernagel, the big question was *how* MHC proteins and viruses are being recognized together by cytotoxic T cells.

In general, cells interact with their surroundings using *receptors* at their surface — small protein molecules that protrude out from the cell — which bind other molecules in their surrounding solution or on other cells.

T Cell Receptor

For T cells, there were two schools of thought. One was that T cells have a *single* receptor that could somehow recognize virus protein and MHC proteins together. The other was that T cells have have *two* receptors, one to recognize the virus protein and one to recognize the MHC proteins.

This debate over the nature of the T-cell receptor was settled by Mark Davis in 1983.

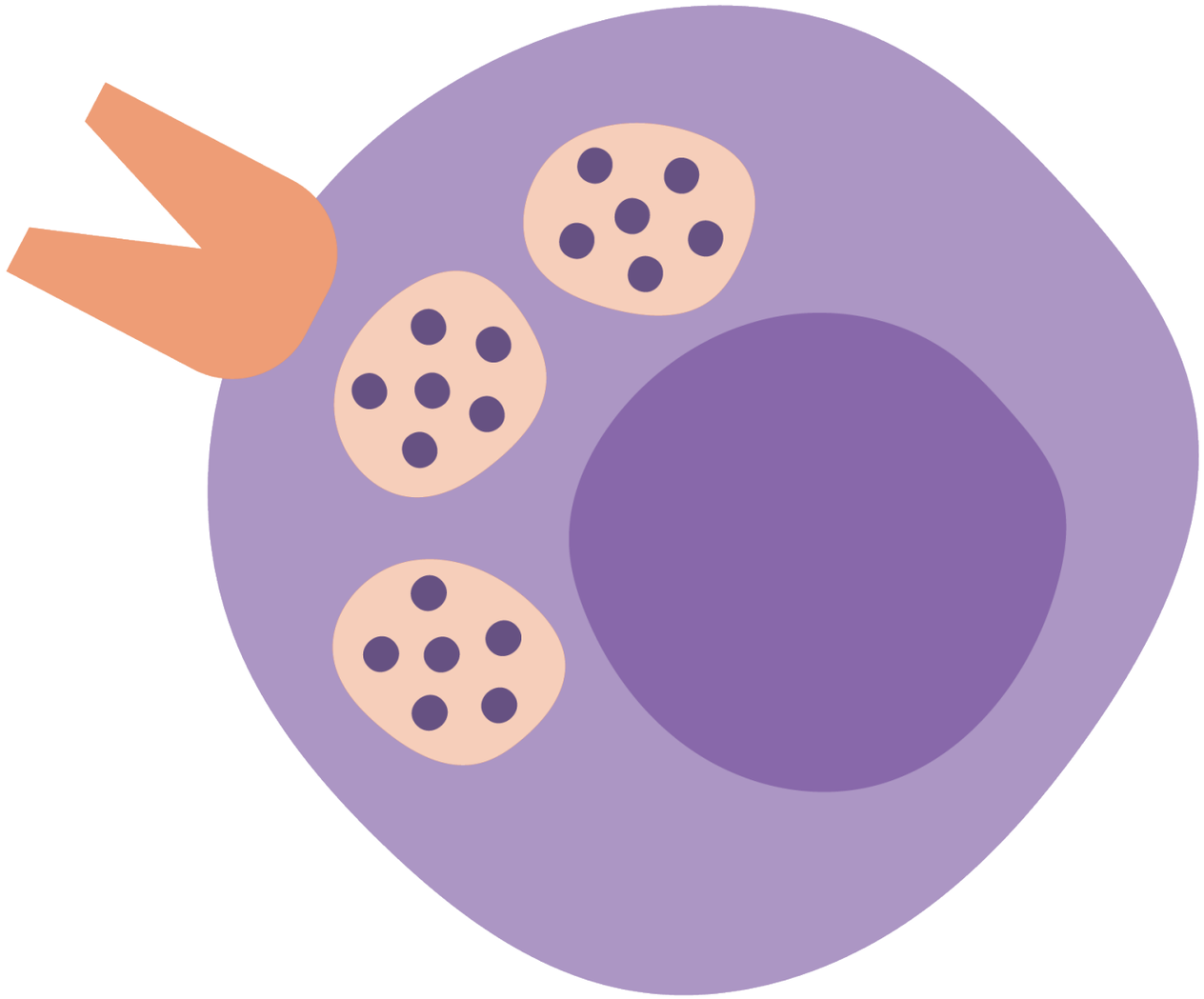
Genetic Diversity of the Immune System

T Cell Receptor

Davis found a gene that was variable between T cells and never found in other cells. So it had to be the main receptor on T cells involved in the recognition of viruses:

There was one receptor that varied from one T cell to the next allowing each T cell to detect one non-self molecule.

T Cell Receptor



Genetic Diversity of the Immune System

This led to a new problem: how was this single T-cell receptor able to recognize the presence of a virus in conjunction with MHC protein?

Again, opinion differed and nobody knew.

The Enigmatic Shape of the HLA Protein

The ultimate and ingenious solution of how T cell recognition works emanated from eight years of seminal research by Pamela Bjorkman, Jack Strominger and Don Wiley at Harvard.

Their work unraveled the full shape of the HLA (-A*02) protein in 1987. The shape of a protein often explains what that particular protein does, and how it does it. For understanding our immune system, the shape of the HLA protein was as revelatory as the DNA double helix.

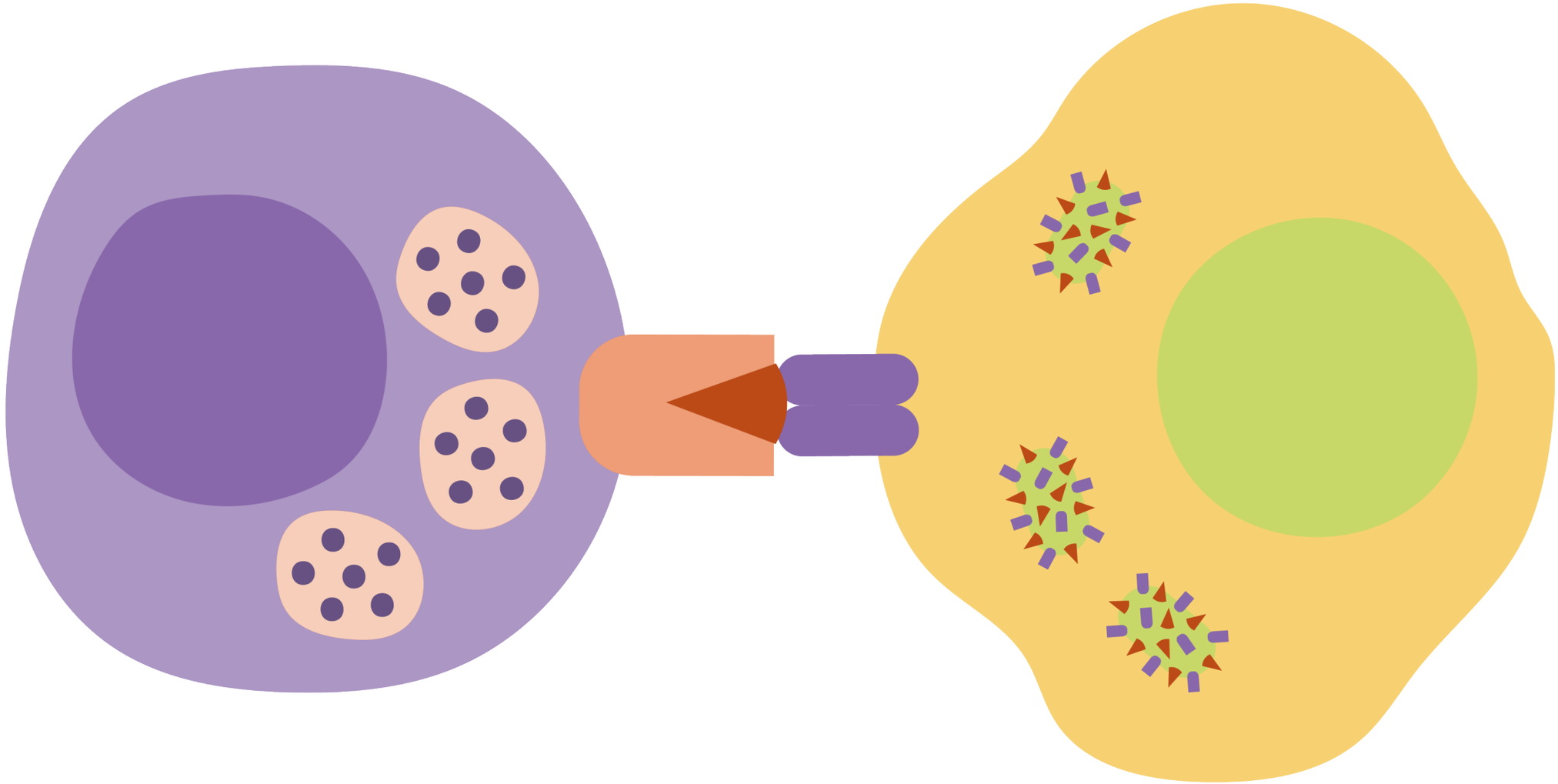
The Enigmatic Shape of the HLA Protein

What the shape of the HLA protein revealed was the following:

The top of the HLA protein has a groove that is perfectly formed for clasping and displaying peptides (short pieces of protein from inside the cell).

All the protein molecules made inside our cells are continually being chopped up into peptides; these are put for display in the groove of HLA proteins.

The Enigmatic Shape of the HLA Protein



The Enigmatic Shape of the HLA Protein

In this way, a cell constantly reports on its surface samples of all the proteins that it is making.

There are about 100,000 HLA proteins on a cell's surface, so collectively they present a good sampling of what is currently being made inside the cell.

T cells use their unique receptors to detect what is being held in the groove of HLA proteins on another cell.

The Enigmatic Shape of the HLA Protein

Any T cell that has a receptor that will be activated by a self-peptide in the groove of an HLA protein is killed off in the thymus. So any T cell let out of the thymus has a receptor that can be activated by a particular combination of peptide and HLA protein.

If one of these T cells gets activated, it must have seen peptide that has never been in the body before.

This, in short, is how self and non-self are distinguished!

Genetic Diversity of the Immune System

Our difference in HLA genes encode for slight variation in and around the groove where the peptide sits: this means each type of HLA gene makes a protein with slightly different shaped groove on top.

This means that each HLA protein presents a different sampling of what's being made inside a cell. And for any particular peptide, only some HLA types of all those present in the population will be good at clasping it. So each person is better or worse at detecting one particular peptide.

Genetic Diversity of the Immune System

HLA proteins that can’t hold on to one particular peptide will have the right shaped groove for others, perhaps from another virus or an alternative peptide made by the same virus.

Some of us will be inherently better than others at defending against a particular infection.

Our immune system has evolved in defense of humanity as a whole — to protect all of us as a species from anything dangerous that could arise.

“Still wrestling with big questions”

At 94, biochemistry professor Jack Strominger is still working in his lab. He will retire and become emeritus in July.

Kris Snibbe/Harvard Staff Photographer

The Harvard Gazette

https://news.harvard.edu/gazette/story/2020/01/jack-strominger-to-retire-after-a-lifetime-of-achievement/

At 94, pioneering scientist Jack Strominger remains at the bench

Interferon-Stimulated Genes

To be continued …