

ACCADEMIA NAZIONALE DEI LINCEI

IMMUNOLOGICAL REVOLUTIONS: FROM CANCER TO GLOBAL HEALTH

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I like to think of the immune system as an extraordinary orchestra, inasmuch as its good functioning generates harmony with the external world, the microbial world that surrounds us, and with our inner world. It is an extremely complicated orchestra, made up of about four thousand billion orchestra members organised in a hierarchical way and with a vast repertoire. Our "inner world" is the microbial world that accompanies us, the microbiome: in a sense, we are made of microbes, since about 90% of the genetic information

found in the human body is made up of this complex world. By this term we mean the billions of microorganisms (bacteria, fungi, viruses) that live in symbiosis in our body, mainly in the intestine, but also on the skin and in the respiratory tree. The harmony with the microbiome depends on our immunological orchestra. However, we must emphasise that we do not know all the musicians, all the instruments and all the repertoires of our immunological orchestra. The dissection of the complexity and functions of the immunological orchestra formed the basis for genuine revolutions, which changed scientific research and medicine.

The immune system and the central nervous system are the two "massimi sistemi" of our body, to use a Galilean term. They are similar in complexity, biological investment, physical weight, and even have some of the same keywords. We know that these two systems communicate, but we do not yet fully know in depth the implications of this ongoing dialogue. The two systems share a key word: recognition. To be able to recognise the good from the bad, the outside world from oneself. Without communication, neither system can function and they also have to communicate with each other. Again, a fundamental shared characteristic of the immune system is memory: immunological memory is the basis of vaccines and we tend to lose it as we age, just as we tend to

lose the memory of our central nervous system.

The immune system is basically made up of two layers or lines of defence. A first line of defence is made up of what, in jargon, is called innate immunity. There are many cells that are part of it: monocytes or neutrophils for example, which we can count when we see a blood test. The characteristic of these cells, among other things, is that they are capable of phagocytosis. Then there are cells that behave like professional killers, with a license to kill: they are called NK cells and Member Lorenzo Moretta has made a fundamental contribution to the understanding of their molecular mechanisms of recognition.

This first line of defence is critical: we estimate that about 90% of daily encounters "with prowlers" – such as viruses or bacteria – are handled by our first line of defence. And here we introduce another metaphor: that of the army. These days it is not pleasant to talk about war, but in our body there is a continuous conflict: it is estimated that about one hundred million of the front-line cells die every day to maintain balance with the outside world.

It has always been thought that the first line of the immune system has no memory, i.e., the ability to "remember" an enemy already encountered and act accordingly. However, recent research has indeed shown that

the first line of defence does have a form of memory, "trained immunity" (which we will encounter later). For example, some vaccines not only give protection against the pathogen with which they are directed, but increase resistance against unrelated microbes.

The first line of defence is essential to usher in and start the second line of defence, much more complex, which is set in motion only when the first line cannot handle problems quickly. The second line is that of antibodies, for example, in jargon: "adaptive immunity". When the first line of defence sounds the alarm, symptoms appear that we can be aware of: pain in the arm, where a vaccine has been injected, redness around a cut, or fever. The latter is a fundamental defence mechanism: for example, the World Health Organization recommends not to overdo it in treating fever in small children. The protagonists of the second line of defence are cells that we call T lymphocytes and B lymphocytes. T lymphocytes are conductors of the immunological orchestra: they decide which weapons to use to counter a problem. B cells produce antibodies. This is an extraordinary ability: our immune system produces antibodies against germs that did not exist in the hundreds of thousands of years of evolution of our species. Or, again, we make antibodies against chemical compounds created by the chemical industry and that do not

exist in nature. An example of this is skin hypersensitivity to metal objects containing nickel. This extraordinary repertoire of the adaptive immunological orchestra is generated by mixing segments of genes and selecting the "rearrangements" that have turned out well, which give rise to a functioning antibody molecule.

2025 marked the anniversary of a great immunological revolution: fifty years ago, two immunologists in the United Kingdom, George Khoeler and Caesar Milstein, conducting fundamental immunology studies, developed a technology to create antibodies in unlimited quantities and directed against a very specific target: monoclonal antibodies. A great revolution in biology and medicine, the first basis from which Precision Medicine was born. Many of the most common diagnostic tests are based on monoclonal antibodies. For example, the PSA test – which males from a certain age may have done for the early diagnosis of prostate cancer – is based on monoclonal antibodies. They have also revolutionised therapy: we use monoclonal antibodies in the fight against cancer, infectious diseases and autoimmune diseases. But that's not all: it is surprising that we use monoclonal antibodies to treat hypercholesterolaemia and migraines that do not respond to traditional drugs. We are, therefore, facing a revolution in Fundamental Immunology that has

transformed Medicine: from cancer to migraine.

As in all orchestras, it happens that the immune system also makes mistakes: the opening, the tonality or even the piece of the repertoire. We can classify immune system errors into four categories:

1) Exaggerating in the response, this is what happens in sepsis;
2) Blaming the innocent, allergy;
3) Hitting the wrong target, causing harm to ourselves, autoimmune diseases;
4) Falling asleep in front of the enemy, cancer.

I will focus on the latter theme, since the development of Immunology and Immunotherapy of tumours has represented a revolution in Medicine and has been part of my scientific life and that of Members such as Lorenzo Moretta, Guido Forni and Franco Locatelli.

Over a century ago, the great fathers of Medicine such as Paul Ehrlich, saw the weapons of Immunology (antibodies, vaccines) begin to change the lives of people all around the world. They saw, for example, antibodies saving children from a horrendous death, that of diphtheria croup, a severe form of bacterial laryngitis caused by *Corynebacterium diphtheriae*. They saw smallpox literally disappear thanks to the vaccine. From that moment, scientists began to try using

immunological weapons against cancer. This vision, this dream, has spanned a hundred years of medical history: it has also spanned my entire scientific life; a dream studded with setbacks.

Following the failures of attempts to use immunotherapy against cancer, at the beginning of the new millennium there was widespread scepticism that the study of the immune system in tumours could have an impact on therapy. A vision of oncological disease that was only centred on the tumour cell prevailed. This widespread feeling at the beginning of the millennium is well represented by a review that had the ambition of defining the essence of what cancer is (Hanahan and Weinberg, Cell 2000). The authors crystallised the essence of cancer in 6 fundamental capabilities (Hallmarks) all centred on the tumour cell. The authoritativeness and sharing in the community of this review is evidenced by its being one of the 20 most cited papers in all the scientific literature.

Many immunologists, including myself, were not of the same opinion, going a bit against the mainstream of thought, and we wrote about it (e.g. Balkwill and Mantovani, Lancet 2001). We still thought that the immune system was important in the process of carcinogenesis and had therapeutic potential to be exploited. We have thus contributed to and experienced

two major changes. The first is a paradigm shift. It has been accepted that cancer is not only the cancer cell but also the ecological niche – we call it the microenvironment in jargon – within which a tumour grows and disseminates.

A clinically evident and metastatic cancer is, in a sense, the failure of the immune system. Every day it eliminates cells that are at risk of becoming cancerous or tumours in the early stages of growth; a clinically evident tumour is the result of escape by selection to this fundamental surveillance mechanism.

The paradigm on which the consensus crystallised in the first 10 years of the century preaches that cancer is made up not only of cancer cells, but also of a complex ecological niche, the microenvironment, of which the cells of the immune system are part and the microenvironment is just as important as the cancer cell itself. In the tumour microenvironment, there are first-line cells such as macrophages, which have literally sided with the enemy. They act as corrupt gatekeepers who aid tumour progression and suppress effective responses. The tumour also includes "professional brakemen": they are the cells we call regulatory T, whose job is to keep the immune system under control. And finally, there are cells that could act against the tumour cell, T and NK cells, but which are held back by corrupt gatekeepers and professional brakemen.

What has been described represented a great change of vision that has been accompanied by the discovery of the brakes of the immune system: the checkpoints. The discovery of brakes is the second major change and has made it possible to develop antibodies that inhibit their function.

Paradigm shift and identification of the brakes have paved the way for the *immunorevolution*, the immunological revolution in cancer treatment. Nowadays, immunotherapy represents a treatment modality, in addition to surgery, radiotherapy, chemotherapy and targeted therapies. One of the challenges we face is to combine these different weapons in an increasingly effective way.

So let's see what the elements of the immunorevolution are.

First of all, vaccines. We must not forget that we have two preventive vaccines against cancer: they are the vaccine against the hepatitis B virus, which is given to children and prevents some liver cancers. The use of the hepatitis B vaccine is one of the reasons why liver cancer is decreasing in our country.

The second preventive vaccine available is the one against the papillomavirus which causes cervical cancer in women and head, neck and anal cancer in males. These are preventive vaccines. The dream, the research effort, is to find

therapeutic vaccines for cancer. We have the hope, supported by very encouraging clinical data, to use personalised therapeutic vaccines, for example, based on gene sequencing and nucleic acid technologies (mRNA vaccines).

The second weapon we have are the antibodies that block the brakes (we call them checkpoints) or block the pedal that presses the brake. A pedal that is often pressed by the corrupt gatekeepers we have talked about. These checkpoint-blocking antibodies have changed the lives of many patients. The story of the first of these, Sharon, a young woman with advanced melanoma destined for hospice, well illustrates the beginning of the Immunorevolution. Pierre Goldstein in Marseille had discovered a gene expressed in T cells and called it CTLA4, but he did not understand its function. Jim Allison discovered that it acted as a T cell brake, but his proposal to experiment with a CTLA4 blocking monoclonal antibody was met with widespread scepticism. Sharon, treated with Allison's antibody, responded completely, which left radiologists at Sloan Kettering in New York incredulous. It was the beginning of the Immunorevolution. Today, immunotherapy is part of the therapeutic weaponry in oncology, but the challenge of the many resistant patients and types of cancer (e.g. pancreatic and ovarian) that do not respond to this therapy remains. In short, perhaps as always,

a still unfinished revolution that continues to represent a research challenge.

The third pillar of the immunological revolution is made up of cell therapies. For many decades we have known that some cells of the immune system are capable of killing cancer cells. Starting from this knowledge, CAR-T cell technology was developed. It takes the patient's cells, those potentially with a "license to kill", engineers them with a new antenna that recognises cancer cells and reinfuses them into the patient. This technology – pioneered by a colleague in the United States, Carl H. June – has changed the lives of many patients with haematological malignancies and beyond, as demonstrated by Member Franco Locatelli for a rare childhood solid tumour. It is a technology based on synthetic biology: for the first time we are using drugs made up of living cells.

Again, the scope of this discovery can be deduced from the example of a patient: her name is Emily Whitehead, she was a child with acute lymphocytic leukaemia. These patients are cured in about 85% of cases with traditional therapies. She was one of those who did not respond to those therapies, and she was cured by CAR-T cells. Right now we use CAR-T cells to treat leukaemia and lymphomas in children and adults and now also multiple myeloma. The hope is that we can use CAR-

T cells to treat solid tumours. A hope and a challenge, because it is much more complicated to use this technology for solid tumours. Furthermore, CAR-T cells also constitute a hope for the treatment of autoimmune diseases.

In general, immunological revolutions are often transversal, crossing the boundaries of different specialisations, as we have seen for monoclonal antibodies and as is happening for CAR-T cells. Again, the Immunorevolution in the fight against cancer is, perhaps as always, an unfinished revolution that continues to represent a challenge for research.

An orchestra has to rehearse and practice, so that it can play in harmony. Well, the same is true for our immune orchestra which must guarantee us health and well-being. There are three pillars to keep our immune system in shape: vaccines, environment and lifestyle.

Vaccines are the medical intervention that has most dramatically changed the life of our species on the planet. They are based on immunological memory: we confront a piece of a microbe or the whole microbe; which can be attenuated and alive, or killed, and thus prepare our immune system for the encounter with the real pathogen. If we are vaccinated, the immune response will be faster in what is a veritable race between us and the pathogen. Our performance

will be faster, higher and more effective. As mentioned, vaccines have been the low-cost intervention that has had the greatest impact on the life of humanity.

Scourges such as polio and smallpox have disappeared largely or entirely on the planet thanks to vaccinations.

The news reminds us, however, that these diseases have not disappeared out of kindness towards our species, but in the case of polio, because we continue to vaccinate. We should remember that in our country, measles caused four hundred deaths a year, especially children, before the introduction of the vaccine. A low-cost intervention: it is estimated that one euro spent on vaccines leads to a saving of twenty to thirty euros. The hepatitis B vaccine, for example, costs the National Health Service more or less sixteen euros and prevents diseases that cost tens or hundreds of thousands of euros, for example chronic hepatitis or liver cancer.

The question we can ask ourselves is this: is it better to get vaccinated or sick to exercise our immune system? All pathogenic germs know the immune system better than all immunologists in the world do, meaning they have been selected to have strategies to suppress the human immune system. So, they know it very well.

Take measles for example: it wipes out immunological memory; it therefore also leaves immunosuppression that

lasts up to two years. This is why measles infection is accompanied in about 20/25% of cases by concomitant diseases, for example infections with other germs, and often requires hospitalisation. Not only that: in about one case in two thousand, measles causes encephalitis, in many of these cases in a very serious form, known as subacute sclerosing panencephalitis. Such encephalitis leaves irreversible damage in the brain. And, in one case out of three thousand, it causes death. In the measles wave in 2017-2018 in Italy, the picture was even worse: over 7900 cases with 12 deaths (https://www.lincei.it/it/vaccini-position-paper). What about vaccination against measles? In one case in a million it causes encephalitis, but it is usually in a mild form that manifests itself with high fever and, in young children, can cause seizures that can be controlled. These data say that the best training is the vaccine, not the natural disease. It should also be added that for vaccines, as for any medical intervention, we must weigh risks and benefits. This assessment is done with particularly care in the case of vaccines, because they are administered to healthy people to prevent and not cure the disease. Vaccines, therefore, are the first form of training the immune system undergoes.

Even for vaccines, doctors and scientists have faced setbacks, accompanied, however, by true technological and

scientific revolutions. For example, a revolution in vaccinology was constituted by the so-called Reverse Vaccinology, whose pioneer was the Member Rino Rappuoli. Rino Rappuoli has changed the way we think about vaccines: he decided not to look at the pathogen, but to look at the sequences of genetic information of the DNA that are present in the pathogen, which encode the pathogen's molecules. Thus, he managed to make a vaccine against Meningococcus type B, succeeding where others had failed.

A more recent revolution is that of structural vaccinology. Here the lesson came from the Respiratory Syncytial Virus (RSV), a scourge for children and the elderly. For fifty years, attempts to make a vaccine against RSV have led to failures. History changed when researchers figured out how to make a vaccine directed against the "flexible hook" (protein F) that the virus uses to attach itself to our cells, stabilising its conformation.

These two examples tell us how technological revolutions have accompanied the development of vaccines. We hope that technological revolutions will help us to create therapeutic vaccines and vaccines against some pathogens against which, until now, we have only failed.

The second pillar to train the immune system is the environment.

An example of an environmental, seasonal factor is for example, nanoparticulate materials, which become a problem especially in winter. Nanoparticulate materials inappropriately activate the first line of defence, causing inflammation not only in the lungs but also systemically. This is the fundamental reason why, during the winter period, in a polluted context, we record an increase in lung disease, cardiovascular problems and the risk of developing certain cancers.

The third pillar is lifestyle. There is a formula that summarises everything we know about lifestyle and immunity: zero, five, thirty. Zero means zero smoking, because smoking – among the many things it does – activates an out-of-control inflammatory response that contributes to increasing the risk of cancer, cardiovascular disease and other diseases. Five means eating fresh fruit and vegetables five times a day because, for example, they activate the sentinel cells of the immune system. We call them dendritic cells: we know that some molecules in fresh fruits and vegetables exercise and train first-line cells.

Finally, thirty minutes of daily exercise are recommended. Exercise not only trains our muscles and cardiovascular system, but also our immune system. Scientists still haven't figured out why exercise is important for the

immune system, but we're increasingly surprised by the impact it has on preventing and treating diseases, including cancer.

Unfortunately, this approximate formula of immunological well-being, and not only that, is associated with a great concern related to the increase in obesity, particularly among children. The World Health Organization has declared an obesity epidemic. But what does obesity have to do with the immune system? Fat tissue is made up not only of lipid cells but also of cells of the immune system that play a fundamental role in this case. When we are overweight or obese, these cells receive excess signals as well as wrong signals; they respond in a confused way, increasing inflammatory tone. And this is one of the fundamental reasons why obesity and excess weight are, for example, a cause of cancer as well as of inflammatory diseases.

Three pillars of keeping the immune system in shape are also accompanied by many challenges. These are scientific and social challenges. For example, we need to better understand how immunological memory works and therefore better design vaccines, as well as predict how long their protective effect will last. All our attempts to make an effective vaccine against HIV have been met with failure. Against the mycobacterium of tuberculosis we're using a vaccine that is

more than a hundred years old and scarcely effective and we haven't been able to improve it. And then there is a social challenge: that of sharing knowledge and immunology weapons such as vaccines, with people in poorer countries. I am very close to the NGO Medici con l'Africa CUAMM and I think of the children in the most fragile countries of the African continent, 1.5 million of whom die because they have no access to the most basic vaccines. I think of the approximately 300,000 women who die from cervical cancer caused by the papillomavirus, especially in sub-Saharan Africa, when an effective and safe vaccine exists. The cuts in Lucio Fontana's canvas well represent the general challenge we face, with the immunological revolutions I mentioned behind us: crossing the dimension of not knowing in order to know, put to the service of the health of individuals and communities, without forgetting perhaps the most difficult challenge, that of sharing with the poorest and most fragile.

Alcune referenze selezionate

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