Laudatio
von
Prof. Dr. Charles A. Dinarello

anlässlich der Verleihung
des Paul Ehrlich- und Ludwig Darmstaedter-Preises
2018

an
Prof. Dr. Anthony Cerami
und Prof. Dr. David Wallach

Paulskirche, Frankfurt am Main
14. März 2018

Es gilt das gesprochene Wort!

Honorable Guests

This is a great day for the Paul Ehrlich and Ludwig Darmstaedter Prize ceremony. Anthony Cerami and David Wallach share this prize because their work and discoveries have greatly impacted basic science and clinical medicine. Working separately on two different hemispheres and coming from two different fields of research, both have contributed to the mechanisms of disease and how we treat disease. When they started their respective projects decades ago, they were not aware that they were working on the same molecule and they never imagined that they would be together in this great historical room rewarded for their contributions on the same molecule. But before explaining their scientific work, a few words about these individuals.

Anthony Cerami is the grandson of poor immigrant families from Italy and Ireland, who came to the United States to seek a better life and future for their children. The career of Anthony is a prime example of how immigrants give so much back to their new country and at the same time, to the world. David Wallach is the son of immigrants who came to Palestine as Zionists, who wanted to escape the persecution of European Jews and in doing so, escaped the Holocaust. David's career is an example of how the children of immigrants flourish in open societies that value education. Today we celebrate the contributions of these scientists but we also celebrate that a career in science is the one field least affected by one's origins but rather respected for one's contributions. Today, we also celebrate the contributions of Paul Ehrlich and Ludwig Darmsteadter and how their careers also impacted basic science and clinical medicine.

What are the contributions of Anthony Cerami and David Wallach? Both made pivotal contributions to the field that is called cytokine biology. Cytokines are small proteins that are active proteins. Most of proteins in our bodies are structural like bones and tissues but cytokines are active molecules. Cytokines are produced by one type of cell and change the activity of other cells. In that sense, cytokines are like hormones such as insulin or thyroid hormone. Another way of looking at cytokines is they are the hormones of the inflammatory and immune systems. Although they served evolution for many millions of years to protect against infections, they make us very sick. Anthony Cerami and David Wallach worked on a cytokine called tumor necrosis factor or TNF. This name tells us that the activity of TNF is to cause necrosis (or death) of tumors. This name is a confusing name because it does not accurately describe all the properties of TNF. More later on how names are difficult to change.

Anthony Cerami was interested in the metabolic changes that take place with chronic infection, and particularly in massive weight loss. Humans lose weight with chronic infections and tuberculosis is a classic example. Look at how opera reminds us of the metabolic costs of tuberculosis in La Traviata and La Boheme as the soprano's waste away before they sing their last aria.

Cerami studied how the metabolic changes are caused by certain enzymes, particularly enzymes that affect mobilization of fats. Fats are used for energy or are stored in fat tissues. One enzyme is called lipoprotein lipase. Anthony's research focused on cytokines that are released from specialized cells called macrophages His experiments showed that there was a small cytokine protein released from macrophages that inhibited the function of lipoprotein lipase. He reasoned that a cytokine produced by an animal or a human with a chronic infection would suppress lipoprotein lipase and the individual would not be able to use fats as energy. Weight loss and self-starvation would take place. Indeed the circulation of patients with chronic inflammatory diseases such as rheumatoid arthritis has high levels of fats in the blood that they cannot use as a source of energy. He then started to purify this cytokine and defined its molecular characteristics.

At this point, he gave this cytokine a name. He called the cytokine "cachectin" because this name related to the severe cachexia or wasting we see in patients. He also reasoned that one should

be able to treat cachexia and other changes that take place in patients with chronic inflammatory disease. For example, he noted that these patients also had the characteristic of low red blood cells and anemia of chronic inflammation such as occurs in rheumatoid arthritis. He then went one pivotal step further and proposed that cachexia and anemia could be reversed if one treated these patients with a monoclonal antibody that blocked the detrimental activity of cachectin. The year is 1981 some 37 years ago. We will return to Anthony Cerami, who continued to work on cachectin and its biological properties.

In 1984, the human gene for TNF was discovered and it was then possible to make synthetic TNF. Having the gene structure of TNF was a milestone in that it allowed for a great increase in experimentation. There would be sufficient amounts of TNF available to study, including making antibodies. Having a plenty of synthetic TNF particularly benefitted those who were interested in how TNF killed tumor cells. Actually, the motivation to find the TNF gene was to produce large amounts of TNF to treat humans with cancer. Many cancer doctors believed that TNF therapy for cancer patients would be "a magic bullet" in that it would kill only the tumor cells and not normal cells. It was reasoned that TNF therapy would not have the problems of chemotherapy and radiation therapy. But there was an early wake-up call. A wake-up call that had great implications for what Anthony Cerami was telling us. What was the early wake-up call? What happened shocked everyone. TNF injected into humans with cancer produced a great deal of sickness and brought some patients close to death. Suddenly, TNF was a very dangerous cytokine. The concept that TNF could be used to treat cancer patients was rapidly losing interest. It would not be possible to treat cancer with TNF without producing a dangerous situation for patients.

Far away from New York City, at the Weizmann Institute in Israel, David Wallach is working on TNF. David wanted to isolate and characterize a naturally occurring inhibitor of TNF. With plenty of synthetic TNF available, David's research program expanded. Many laboratories working on how TNF killed tumor cells but David Wallach was interested in the inhibition of TNF. He believed that knowing how TNF killed cells, one could understand the intracellular machinery of cell death. Using a laboratory method of TNF-induced cell death, he sought to isolate this natural inhibitor of TNF and reasoned that this natural inhibitory substance would lead him to how TNF worked.

This inhibitor of TNF was found in the urine. Therefore, David organized volunteers of men at Weizmann Institute to collect their urine. One can imagine the unpleasantness of collecting of liters and liters of urine but the Wallach laboratory was dedicated to this project and worked hard to isolate this TNF inhibitor. The urine had to be concentrated, another unpleasant process. But larger and larger amount of urine were required. Isolating a single protein from the several hundred that are in human urine requires many tries and there would be many failures. The good news is that David and his laboratory were indeed successful in isolating the TNF inhibitor. They isolated and purified a single molecule that inhibited TNF and called the molecule "TNF Binding Protein".

Now the story continues in Rome, Italy. Not far from the Vatican, there is a new source of urine and it is already concentrated. This new source of urine contains the TNF inhibitor along with hundreds of other proteins. Now for something you did not expect to hear. The urine was donated by post-menopausal Italian nuns. That's right, Italian Nun Urine. The nuns donated their urine (thousands and thousands of liters) because the urine of post-menopausal women contains hormones that increase ovulation. These hormones are needed to help ovulation in some women who want children but are having difficulties. Of course, the primary motivation for the nun's donation of their urine was to help women have babies, but they did not know that their donations will also advance medicine and the treatment of disease. Thousands and thousands of liters of nun urine was concentrated and the hormones extracted. The extracted hormones were turned into a drug (called Pergonal by the company Serono) and many people today all over the world owe their existence to the

urine of these nuns. Fortunately, after extracting the hormones, the residual urine was frozen in freezers in Rome.

Now back to Israel where the urine arrives at the Weizmann Institute. The bonus in Israel was that once the hormones were extracted, the residual nun's urine contained large amounts of the TNF inhibitor. Wallach's isolating the TNF Binding Protein was a milestone. He now knew some of its structure. There is no doubt that isolating the TNF Binding Protein and knowing its structure was a milestone. But the story goes on further. Fellow Weizmann Institute scientist Dr. Daniela Novick, the daughter of two Auschwitz survivors, found that there was a second TNF inhibitor in the urine. The structure of this second TNF inhibitor was different.

So now Wallach had two different inhibitors to compare, TNF Binding Protein-1 and TNF Binding Protein-2. What were these TNF Binding Proteins and how did they work? These two TNF Binding Proteins are, in fact, partial segments of the TNF receptors. Although those working on TNF predicted that TNF activated a cell surface receptor, none was known at the molecular level. Therefore, what started out as a project to isolate a natural inhibitor of TNF resulted in a breakthrough to understand how the body controls a complex mechanism such as cell death. David Wallach gave the scientific community the key to unlock how TNF works. The implications for this discovery provided a treasure chest of knowing how the outside world of the cell affects the inside world of the cell.

We will come back to Israel, but now back to New York City and the Rockefeller Institute. Anthony Cerami's laboratory is busy with the purification of cachectin. They want to know the exact physical composition of cachectin in order to understand how it works and how cachectin accounts for disease. Bruce Beutler working in the Cerami laboratory continued with the methods of Cerami and Kawakami and purified cachectin to a single molecule. But now comes the surprise that no one expected. The amino acid sequence of purified cachectin matched exactly the amino acid sequence of TNF. Thus TNF and cachectin are the same molecules. The year is 1985. No one expected this. Cachetin being the molecule as TNF instantly meant that the properties of cachectin in infectious and inflammatory diseases was the same for TNF. At this point, many scientists in this field believed that the name TNF should be changed to cachectin. But the TNF mafia was not giving up and the name TNF is used today for a cytokine that causes inflammation. Today TNF is primarily known as an inducer of disease, an inducer of the metabolic upheaval of infections and an inducer of inflammation. But the implications that TNF was an inducer of inflammation also meant that the two inhibitors of TNF that were isolated from the urine could be used to inhibit inflammation.

Anthony Cerami told us in 1981 that we should treat rheumatoid arthritis with monoclonal antibodies to neutralize cachectin but since cachectin is TNF, rheumatoid arthritis can be treated with antibodies to TNF. This was exactly what happened next. Monoclonal antibodies that were initially produced to block TNF in patients with severe infectious sepsis were tested in patients with rheumatoid arthritis. Indeed, those studies proved that Anthony Cerami was correct. Antibodies to TNF became a new therapy to treat rheumatoid arthritis, a painful crippling disease. Today antibodies to TNF are used to treat two other terrible diseases, inflammatory bowel disease and psoriasis. I would like to add at this point that important discoveries in science are sometimes claimed by others who did not contribute to the fundamental discovery and that is why we honor Anthony Cerami today for his vision.

Now back to Israel where this amazing story has one more chapter. David Wallach's two TNF inhibitors are the external segments of what is termed TNF Receptors. Receptors mean exactly that: they "receive" information and then transmit the information to the inside of the cell. So the two inhibitors of TNF are the two TNF Receptors. The part of the TNF receptors that ends up in the urine is the part that inhibits the activities of TNF. The same molecule that sends the signal to the cell to start inflammation, also provides a segment to block inflammation. Thus, from the discovery of the two TNF

inhibitors a new concept emerged; inflammation is the result of the balance between the agonist part of the TNF receptor and the antagonist part of the receptor, both being from the same molecule. This is a classic example of the efficiency that nature. Nature gives more than one function to a single gene. The part of the TNF receptor that inhibits TNF is now a drug. Enbrel is the name of the drug, which is made from the second TNF receptor found in the urine.

How does this story end? The scientific community and countless numbers of patients have benefitted greatly from the vision and dedication of these two scientists, their students and their collaborators. Working separately in two different parts of the world, working separately with two different goals, we know so much more about TNF, how TNF receptors function, how TNF causes disease and how to treat TNF-mediated diseases.