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Awarding of the honorary degree in Medicine and Surgery

James P.Allison
10th of October Laudation

Advisor: Vincenzo Bronte

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Magnificent rector, authorities, distinguished colleagues, students, ladies and gentle-men, the awarding of an honorary degree is an honorary title granted to those who have distinguished themselves for their works, intellectual contributions or scientific merits and, therefore, represent exceptionally deserving individuals.

Altogether, the Department that proposes it and the University that proclaims it have come together to offer the community the necessary emphasis on the goals achieved by people who, through know-how, competence and skill, have represented examples to follow, paving innovative paths in which they have established themselves as guides and benchmarks.

And it is for this purpose that the Magnificent Rector and the Director of the Depart-ment of Medicine have assigned me the task of motivating the recognition of the hon-orary degree in Medicine and Surgery to James Patrick Allison, better known to friends, patients, doctors and scientists as Jim.

I am particularly grateful for having been given the honor of introducing you to a teacher and friend. A further privilege comes from the opportunity to share this "lau-dation" with you, in the same room where I teach Immunology to students of Medi-cine, some of whom are present in the audience.

The story of Jim Allison can be summed up in the visionary and stubborn quest for the cure for cancer that many researchers commonly share. Today Jim Allison is known all across the scientific world as the winner of the Nobel Prize for Medicine 2018 for the discovery of the role of the immune system in the fight against cancer.

Jim Allison was born on August 7, 1948, in a city in Texas called Alice, a city with less than 20,000 inhabitants that gave birth to another Nobel Prize winner, Robert F. Curl Jr., who won it in 1996 for Chemistry. Alice is also the place where the "Tejano", a unique Tex-Mex music genre, took root in the 1940s. It is precisely the Tejano genre that may have inspired Jim Allison to learn how to play the harmonica, with which he still performs in concerts during parties and events, together with a

group of other in-ternationally renowned scientists who call themselves "The checkpoints", parodying with a note of self-irony Jim Allison's crucial scientific discovery that I will be exhib-iting shortly.

After graduating from high school at the age of 16, Jim Allison enrolled at the Universi-ty of Texas in Austin, where he would then earn a Bachelor degree of Science in Mi-crobiology in 1969 and then a PhD in Biological Sciences in 1973.

The intense passion that aroused his interest in applied and therapeutic science was truly ignited by the premature death of his mother, which occurred when Jim Allison was only 11 years old.

His career and subsequent career path were marked by his entrance into the PhD school when he convinced his supervisor to introduce the study of cancer in the la-boratory. It was a moment of great interest in immunology because the T cells of the immune system had just been described.

T lymphocytes are white blood cells that have peculiar properties: although the lym-phocytes that spot different foreign antigens are only few, once the identification is performed these cells proliferate intensely, multiply and acquire the ability to elimi-nate the source of the antigen. Few soldiers can, therefore, give rise to real armies, ready to battle against the agents that invade our body, clones equipped to best keep us healthy, a role assigned by the evolution of the species to distinguish friends from enemies.

Although the time was appropriate, we should mention that the context in which Jim Allison's research took place was not the easiest.

Immunology was not yet considered a real science and the idea that the immune sys-tem could defeat cancer was regarded with much skepticism, especially by classical oncology. As a matter of fact, a vision centered on the malignant cell as an isolated universe persisted, endowed with unique properties that allowed it to survive despite what was happening in the neighboring healthy tissues.

The pharmaceutical industry experimented drugs to more or less selectively hit mo-lecular targets within cancer cells. The theory of "immunosurveillance", independent-ly proposed in the 1950s by M.F. Burnet and L. Thomas, claimed that the immune sys-tem spotted cancer cells as enemies and activated to attack them in the same way as it attacks foreign agents. Nevertheless, a series of laboratory experiments had reduced and made the formulation of the theory controversial, relegating the role of the im-mune response to the mere control of viral and bacterial infections that can cause cancer, a minority of cases compared to infectious aetiology free tumors.

To sum up, tumor immunology was considered a constant promise on a par with a lush tree that would never bear fruit, an opinion that was still circulating in academic and pharmaceutical circles until a few years ago. Allison focused on the potential of the immune system against cancer.

His doctoral dissertation already proposed a new approach to the treatment of leu-kaemia at the time, but it would still take decades before a drug was patented. Soon af-ter attaining his PhD, Allison began to travel around the United States to further study T-cells.

After an evaluation of the American institutions open to innovative research, Jim Alli-son initially joined the Scripps Clinic and Research Foundation in San Diego from 1974 to 1977. During these years, Jim Allison was committed to studying the struc-ture and properties of MHC molecules, strategic proteins for the activation of T lym-phocytes, expressed mainly by dendritic and macrophage cells and which have the task of presenting the antigen to T lymphocytes.

In 1977 he returned to Texas, to the recently opened MD Anderson Center in Smith-ville, where he could teach and carry out experimental research. Like many research-ers in the field of immunology, Jim Allison thus found himself thoroughly involved in the competition of identifying the means by which a T lymphocyte spots an invading agent. His research led to a publication in "The Journal of Immunology" in 1982, where he described an antibody that spots a molecule on T lymphocytes that, only af-ter two years, will be identified as the receptor for the antigen, the so-called TCR, re-ceptor of the T cell. This is probably the first major contribution to the history of im-munology of young researcher Jim Allison.

After a year at Stanford as an "external researcher", Jim Allison transferred to the Uni-versity of California Berkeley as Professor of Immunology and Director of the Cancer Research Laboratory (1985-2004) and simultaneously was appointed Professor at the University of California San Francisco (UCSF) in 1997. This was perhaps one of the most fruitful periods of his career because during this time he developed a scientific "turning point".

By the 1980s, new treatments based on factors produced by immune system cells, such as interferon and interleukin 2, had raised hopes for effective cancer therapies. However, the high expectations were not met because of the small number of clinical responses and the frequent severe side effects of systemic treatment with these bio-logical drugs.

Some immunologists stubbornly continued to study the role of the immune system in the fight against cancer and their efforts had led to the first identification of tumor an-tigens shared by tumors, molecules spotted by the immune system and manifested mainly by tumors of different histological origin.

A new wave of studies therefore focused on the development of vaccine therapies ca-pable of activating and expanding T lymphocytes clones identifying shared tumor an-tigens. Although these experiments were conducted by excellent research groups and proved functional in pre-clinical animal models, the first cancer vaccines resulted in few objective clinical responses in patients. Enthusiasm for immunotherapy had again declined on the basis of unsatisfactory clinical results.

Towards the end of the 1980s, knowledge of T lymphocyte activation spread out con-siderably and it was discovered that their initial activation required not only the iden-tification of the MHC-associated antigen, mediated by the TCR molecules, but also a second co-stimulus signal, dependent on the interaction between the CD28 molecule on T lymphocyte and the B7 molecule on the antigen-presenting cell. Jim Allison and collaborators actively contributed to the expansion of this knowledge.

Together with the other immunologists who supported immunotherapy, they discov-ered that precisely because of the co-stimulus, T lymphocytes specific for a tumor an-tigen would never be activated through an initial encounter with a tumor cell, but could even be made "anergic", or paralyzed. The majority of tumors, in fact, do not ex-press the co-stimulatory molecules B7 and, consequently, do not turn on the CD28 re-ceptor signaling necessary for full activation of the T lymphocyte.

In this way, tumours are essentially invisible to T lymphocytes, unless dying tumor cells release antigens that are captured by the dendritic cells surrounding the neo-plastic tissue. Dendritic cells are fully equipped with co-stimulatory molecules and, therefore, can activate anti-tumor T lymphocytes. In line with these findings, many therapeutic vaccines included in their formulation both antigens and dendritic cells and/or agents that increase co-stimulatory signals.

In the 90s CTLA-4 was discovered, a protein homologous to CD28 and equally ex-pressed on the surface of T lymphocyte. Misled by the molecular similarities, several immunologists hypothesized that CTLA-4 was another accelerator of the immune sys-tem, but Jim Allison went in the complete opposite direction. He insisted on research-ing and carrying out the "killer experiment", a concept I will resume later below.

He, therefore, demonstrated that CTLA-4 acted as a brake (or inhibitory molecule) on lymphocyte T, rather than as an activator.

It was discovered that the activation of T lymphocytes by the antigenic recognition mediated by the TCR/MHC-antigen contact associated with the co-stimulus CD28/B7, was followed not only by the induction of genetic programs of proliferation and func-tional differentiation but also a parallel program of response blocking, mediated by the increased expression of the molecule CTLA-4. A checkpoint for excessive cell stimulation: a "checkpoint".

In the following years, Jim Allison and his collaborators found a way to free T lym-phocytes from the inhibitory brake imposed by CTLA-4. In fact, in pre-clinical mouse models, as well as CD28 blocking antibodies inhibiting tumour-specific responses, CTLA-4 blocking antibodies were able to increase them. Treatment with monotherapy anti-CTLA-4 antibodies caused complete tumor rejection and induced

long-term im-munity. This was the "breakthrough" I mentioned earlier, namely the discovery of a new way to fight cancer, which focused on the immune system and not on direct ma-nipulation of cancer cells.

In the following years, the perhaps toughest challenge began: persuading colleagues in the medical and pharmaceutical community to produce the drug and initiate clinical studies on cancer patients.

Jim Allison moved back to New York City with his laboratory, due to its proximity to leading pharmaceutical companies such as Bristol-Myers Squibb and Pfizer, and med-ical institutions such as the Memorial Sloan Kettering Cancer Center.

In 2004 Allison became Director of the Ludwig Center for Cancer Immunotherapy. In the following years, he also became affiliated with Weill Cornell Medicine, Weill Cor-nell Graduate School and Howard Hughes Medical Institute. He founded immunology departments there and continued his research, but above all, he managed to oversee the first clinical studies with Hypilimumab, the human anti-CTLA-4 antibody.

Finally, in 2011, Ipilimumab became the first drug in the class of immune checkpoint inhibitors approved by the U.S. Food & Drug Administration (FDA) for the treatment of late stages of melanoma - commercially known as "Yervoy". In 2012, Jim Allison returned to Texas, moving to the MD Anderson Center at the University of Texas in Houston, as a professor and head of the Department of Immunology and Executive Di-rector of the Immunotherapy Platform.

Jim Allison has become one of the most acclaimed immunologists on the planet. In October 2018, a phone call from the Karolinska Institutet in Stockholm informed him that he would share the Nobel Prize for Medicine with Tasuku Honjo of the Japanese University of Kyoto, a colleague with whom he had previously shared the Tang Prize in 2014. The Nobel Prize motivation stated: "They understood that the immune sys-tem can be stimulated to attack cancer cells, a completely new therapy mechanism in the fight against a type of disease that kills millions of people every year and that is one of the most serious threats to the health of humanity".

Recently, I came across statements by Phil Needleman, a scientist who has spent sev-eral years in the pharmaceutical industry: "While great science is an important foun-dation, the true strength of the pharmaceutical industry is in the inventions required in generating clinical proof of concept (PoC) and development of new prod-ucts. Those tend not to be what Nobel's are about, but then again Nobel's don't help treat patients". I must express my disagreement. The work of Jim Allison and his col-laborators proves exactly the opposite, and another example is witnessed by Jim's wife, Pam Sharma, present at this ceremony, who daily matches the highest level of science with clinical practice in the ward. The reason why I added the previous quote is that, despite the diversity of ideas, Needleman shares with Jim Allison a concept that he explored during a meeting we had with young researchers from a biotechnolo-gy company. Jim Allison urged the audience of future scientists to carefully design and ponder the "killer experiment".

There are various meanings to the interpretation of the killer experiment: I believe that for Jim Allison it is the crucial experiment that puts an end to the previous conjec-tures, proving its inaccuracy and initiating an unexpected and countercurrent direc-tion that allows you to achieve new goals. This is an important legacy for all young people who approach science, some of whom are present in this room, a concept that reaffirms the relevance of the creative decision of the researcher at a time when tech-nological massification tends to reduce scientific discovery to the mere observation and description of complex events.

The scientist must be able to synthesize and demonstrate the causality of events, just as Galileo Galilei taught us a few centuries earlier. This episode also outlines another aspect of the figure of our graduate: Jim Allison is also an educator who has never spared himself to attend conferences around the world, promoting immunology with presentations and concerts, always available in the interaction with curious young people who approached him to ask questions.

The effectiveness of the checkpoints inhibitors in clinical trials has succeeded in convincing even the most skeptical cancer immunotherapy detractors.

The stories of patients whose lives have been significantly prolonged by immuno-therapy have become public knowledge in the field of cancer therapy. The impact of Jim Allison's findings could be told with numbers and statistics on the increase in the life expectancy of cancer patients but, instead of scrolling through lists and data, I would prefer to tell you a clinical story that involved me closely.

In April 2015, a colleague from the University's Faculty of Medicine was diagnosed with skin melanoma with metastases in the sentinel lymph node of the left axillary region. It undergoes surgical enlargement in the dorsal area and axillary emptying but, in 2017, new metastases are diagnosed in several locations. Immunotherapy with pembrolizumab began in the same year but had to be discontinued due to the appear-ance of new lesions, treated with radiotherapy and chemotherapy. However, his de-termination to pursue immunotherapy, strongly supported by his wife, also a doctor, led him to research and identify new clinical studies. In 2018 he joined a multicenter study based on the combination of pembrolizumab and anti-LAG3, two antibodies that spot different "checkpoint" molecules.

Our colleague is responding to the new immunotherapy and has been able to resume his academic activity.

Although individual cases should be considered with caution before attributing bene-ficial effects to each specific treatment, this story attests to the growing confidence in immunotherapy and the possibility of clinical responses even in advanced stages and long periods, which would have been inconceivable in previous years.

Finally, many patients with different neoplasms, not just melanoma, have a range of treatment options. The accomplishment of this revolution is almost exclusively due to the "checkpoint" based immunotherapy, which allows, in the luckiest cases, the complete regression even of aggressive neoplasms and advanced stages.

As proof of this, nowadays in medical oncology congresses, immunotherapy has be-come the predominant pivotal topic of discussion.

The current immunotherapies do not cure everyone, we must reassert this clearly, and the way ahead of researchers is still long and will engage us further in the coming years. However, I would like to confirm that the current successes of immunotherapy stem from a precise and careful decoding of basic biology, which has lasted many years, and has taught us that, although we are increasingly in a hurry to turn biological discoveries into life-saving drugs, we must never lose sight of the study of the biolog-ical basis of pathological processes, in order to come up with new and increasingly ef-fective interventions.

I would like to finish by thanking Jim Allison for revealing the enormous power of the immune system against cancer.

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