The Pezcoller Foundation

Journal

Summary

News from the
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November 2015
Editorial

I'm glad to remind you that dr. James Allison was the winner of the 18th Pezcoller Foundation-AACR International Award for Cancer Research. I have also the opportunity to inform that the 2015 Pezcoller Symposium entitled "Challenging Roadblocks to Cancer Cures" took place in Trento June 18-20, co-chaired by David Livingston, Angelika Ammon, Anne-Lise Børresen-Dale, Massimo Loda, Stefano Piccolo, William Sellers and Enrico Mihich with the participation of a significant number of outstanding speakers.
The speakers were: David Baltimore, Mariano Barbacid, Jose Baselga, Scott Biller, Carlos Caldas, Nora Disis, Stephen Elledge, Michele De Palma, Carl June, Marcos Malumbres, Kornelia Polyak, Arlene Sharpe, Rocio Sotillo, Charles Swanton, Ashok Venkitaraman, Antonella Viola, Beth Weaver, Giovanni Scitia.
The Symposium was attended by many young researchers from the main European and Italian schools and laboratories.
During the sessions we gave the Pezcoller Begnudelli Awards to Eleonora Grisard from the National Cancer Institute of Aviano and University of Padua -Ph.D. School in Biosciences and Biotechnology; Riccardo Taulli from the Department of Oncology , University of Turin and Luigi Pausini from Laboratory of Transnational Genomics, University of Trento - Centre for Integrative Biology (CIBIO).
On October 23 2015 in Rovereto we gave the Pezcoller Foundation- ECCO Recognition for Contribution to Oncology to dr. Klaus Meier who gave his scientific lecture in Vienna a few weeks before .
Dr. Meier, whose lifeworks are illustrated in the short report in the following pages, gave his speech describing his activities during the last decades in the recently restored Conference Hall of the Palazzo Istruzione in Rovereto.
The ceremony was attended by Authorities, medical doctors and pharmacists who could applaud at the end also the outstanding performance of a young harpist Ludovica Fierro.
In this issue we are also glad to present the next 28th Pezcoller Symposium "Initial Steps on the Route to Tumorigenesis" .

Gios Bernardi
Editor and President Emeritus

Picture on front page: 2015 Pezcoller Foundation - ECCO Recognition for Contribution to Oncology / Dr. Klaus Meier

2015 Pezcoller Foundation-AACR International Award Acceptance Speech

Immune Checkpoint Blockade in Cancer Therapy

James P. Allison
Chair, Immunology Department, MD Anderson Cancer Center, Houston, TX

I am humbled to receive the Pezcoller Foundation-AACR International Award from the Pezcoller Foundation, humbled to be selected to join the illustrious scientists who have received this award in the past. I thank the Committee for selecting me for this prize, and pledge that I will continue my efforts to make contributions that will justify this honor. I feel that this award recognizes not only my work, but also recognition of the efforts of many investigators and clinicians to establish immunology as a pillar of cancer treatment. The idea that the immune system could fight cancer was first proposed by Paul Ehrlich in the early 20th century and by the 1960s the idea that it might be possible to use the immune system to eliminate cancer and provide long lasting protection against recurrence was under active investigation. Although there were many ups and downs in the field, in the last few years with advances in our knowledge of fundamental mechanisms of the cellular immunity this has become a reality.

Active mobilization of the immune system, especially T cells, the warriors of the immune system, to attack cancer offers three unique features compared to other treatment modalities. The first is the specificity of T cells for unique antigens, many generated by the process of carcinogenesis itself, that are not found in normal cells. The second is adaptability – the immune system can respond to changes in the tumor by activating T cells with new specificities that can recognize new mutations that might make tumors resistant to targeted therapies, for example. And perhaps the most important feature of the T cell response is memory. After a T cell response there are a small number of self-renewing cells that can persist for a lifetime, and provide a rapid response if a tumor recurs.

In the 1980s the demonstration of tumor antigens in human melanoma led to strategies employing therapeutic vaccination to mobilize the immune system to attack cancer. Unfortunately there were few successes. The failure to induce effective immune responses by attempting to turn T cell response "on" with vaccines led many to become skeptical of the potential of immunotherapy.

Consideration of the complexity of fundamental mechanisms that regulate early aspects of T cell activation may provide one of many possible explanations for the limited effectiveness of these early vaccine trials. By the late 80s it was known that engagement of the antigen receptor (TCR) by antigen was not sufficient for T cell activation - additional signals provided by B7 molecules on antigen presenting cells were also required, and these costimulatory signals can only be provided by very cells called antigen presenting cells (APC). When the B7 molecules on the APC engage the costimulatory receptor CD28 on the T cells simultaneously with TCR engagement, an event that can be likened to pressing the gas pedal on a car, the T cells become activation, start dividing at a very high rate, and differentiate into an army of warriors that move through the body to eliminate the invader, be it a virus infection, or, indeed, a mass of tumor cells. However, in

the early 1990s Jeff Bluestone's lab and mine showed that T cell activation resulted in the production of a molecule called CTLA-4, which like CD28 binds the B7 molecules but eventually turns the T cells off. Based on our knowledge of the function of CTLA-4, I proposed that blocking its interaction with the B7 molecules might allow T cell responses to persist sufficiently to achieve tumor eradication.

Our proposal of CTLA-4 as a strategy for cancer therapy was radical in two ways. First, it ignored the tumor cell and focused instead on treating the immune system. It was not necessary to know what the T cells would be directed against, or even the kind of tumor. If it worked, it should work against any kind of tumor, because tumors all express antigens that are not found in normal cells. The second departure from the paradigm was that it was not aimed at turning the immune response on, that is harnessing the immune system to attack cancer, but rather at unleashing the immune system to do so. A corollary of this is that CTLA-4 blockade could unleash T cells primed by tumor cell death that accompanies treatment with cytotoxic therapies, including radiation, chemotherapies, and targeted therapies, or those elicited by vaccination with tumor antigens. Our hypotheses were confirmed in a large series of pre-clinical studies in many different mouse tumor models showing that injection of antibodies into tumor-bearing mice either alone, or in combination with vaccines, radiation, or chemotherapy, could lead to tumor eradication and long lived immunity.

In the late 1990s we teamed up with Medarex to make antibodies to human CTLA-4 for human clinical studies. In early trials the antibody, called ipilimumab, showed objective clinical responses in many cancer types, including melanoma, kidney cancer, prostate cancer and others. In 2010 a large, randomized, placebo controlled trial of ipilimumab showed an increase of 4 months in median survival in metastatic melanoma patients, something that had never before been observed with any treatment of any type. But the most important outcome was that about 22% of the patients were alive 4.5 years after treatment and recent follow up studies showed that these responses could last for a decade and more.. In 2011 ipilimumab was approved by the US Food and Drug Administration (FDA) for the treatment of metastatic melanoma and it is now a standard of care for that disease. A recent follow up study of almost 5,000 metastatic melanoma patients showed that a little over 20% were alive 10 years after treatment with ipilimumab.

While CTLA-4 was the first identified, we now know that there are more immunological checkpoints. In 2001 it was shown that a molecule called PD-1 also inhibits T cell function, but in contrast to CD28, PD-1 interferes with antigen receptor signaling. Like anti-CTLA-4, anti-PD1 antibodies have shown effectiveness against a variety of tumor types in early clinical trials. Two different
antibodies to PD-1 have now been approved by the FDA for treatment of metastatic melanoma, and one of these have also been approved for the treatment of lung cancer.

Since CTLA-4 and PD-1 have different mechanisms of action, it seemed that blockade of both pathways together would be more effective with either alone. A trial of combination treatment with both anti-CTLA-4 and anti-PD-1 showed responses in over 50% of patients, with 2-year survival of even more patients
In the last few years, at least 5 additional checkpoints have emerged and are in either in preclinical or early clinical development, so there is still a lot to do.

Clearly, immune checkpoint blockade is now a pillar of cancer therapy. Among the most exciting developments in the field now is the beginning of development of rational combinations of checkpoint blockade with conventional therapies, and with adoptive T cell therapies. Success to date brings optimism that there will soon be cures for at least some types of cancer.

Pezcoller Foundation Seminars

Meetings on clinical-oncological issues and updates, organised for family practitioners and for doctors working in Italian hospitals.

23rd Pezcoller Seminar

Surgical and molecular pathology of the lung

Slide seminar on neoplastic and non neoplastic pathology with clinico-pathological correlations

Meeting of the Italian group of pulmonary pathologists

September 21 and 22, 2015 Trento – Italy

Unit of Surgical Pathology , S. Chiara Hospital, Trento, Italy

The meeting is aimed for general pathologists and for those with a specific interest in lung pathology. The aim is to provide some lectures with a clinic-pathologic view of lung disease, followed by informal and inactive microscopic workshops, focused on case presentations. All participants are invited to contribute to the case discussions in an informal and constructive way.

24th Pezcoller Seminar

Slide seminar in gynaecological pathology with clinico-pathological correlations

October 29 and 30, 2015 Trento – Italy

Unit of Surgical Pathology , S. Chiara Hospital, Trento, Italy

The meeting is aimed for general pathologists and for those with a specific interest in gynaecological pathology. The aim is to provide a series of lectures with a clinic-pathologic view of gynaecological tumour pathology followed by informal and inactive workshops. These workshops will be focused on case presentations by the faculty. All participants are invited to contribute to the case discussions in an informal and constructive way.

25th Pezcoller Seminar

The irradiation after a previous course of radiation therapy: theory, clinical practice and perspectives

November 28, 2015 Trento – Italy

Proton Therapy Center, APSS

The seminar focused on re-irradiation (a repeat course of radiotherapy to a previously irradiated volume).
The seminar hosted the most relevant national experts in the field (medical doctors and physicists) with the aim to discuss the recent clinical, radiobiological and technological advancements in this setting, including the potential role of hadrontherapy to increase the therapeutic ratio of re-irradiation.
Re-irradiation is considered a challenging therapeutic option which might provide worthwhile clinical benefit in terms of palliation or sometimes even cure to cancer patients who develop loco-regional relapse or second primary tumours.
Local and/or regional recurrence and metachronous primary tumor arising in a previously irradiated area are rather frequent events in some neoplastic disease and in particular in patients with head and neck, brain and pelvic disease. Re-treatment is often associated with an increased risk of serious toxicity and impaired quality of life (QOL) with an uncertain survival advantage. Patients with recurrent tumor after previous radiotherapy may however be considered for salvage reirradiation using different techniques. The decision about which treatment, if any, to use has to be based on the initial characteristics of the disease, relapse patterns and the natural history of disease offering an individualized approach.

In the first two sessions of the Seminar dedicated to general themes several clinical, biological and technical issues were discussed. The need of a thorough clinical evaluation of the patients with a careful selection of the candidates to reirradiation was stressed. Specific attention was dedicated to the need to have available a complete dosimetric information about the previous treatment plan and to the possibility of the new systems to perform a non-rigid deformation to adapt the anatomic contours of the first and second treatment plan. The updates in radiobiology related to the constraints of different tissues exposed to radiation and on fractionation were also reported. Particular interest was raised by the new indication of the use of particles (protons and carbon ions) for reirradiation thanks to the favourable specific ballistic characteristics of these beams.

The second part of the Seminar in the afternoon was reserved to a survey of the most frequently treated (irradiated) sites of recurrent disease. The following brief paragraphs summarize the reported conclusion:

Head & Neck: Whenever feasible, salvage surgery is the method of choice for curative intent in patients with H&N tumors. Reirradiation, administered either with or without concurrent systemic therapy, is feasible and tolerable in properly selected patients with recurrent or a new primary tumor in a previously irradiated area, offering a meaningful survival (in the range of 10% to 30% at 2 years). Long-term disease-free survival has been observed, albeit with the risk of significant, possibly life threatening, late complications. Intensity-modulated radiotherapy (IMRT) has been shown to be able to reduce toxicity and improve disease control. The use of particle therapy in this setting is increasingly proposed in order to reduce the risk of complications. . A careful selection of the patients is however mandatory.

Rectum: Many patients with rectal cancer receive pelvic radiotherapy as a component of a multimodal approach for the treatment of their primaries. Although local recurrence is infrequent, reirradiation may be needed to improve resectability and outcomes or, if surgery is unavailable, to offer a good palliation. The literature shows that reirradiation of rectal cancer to limited volumes is feasible. The use of particle therapy in this setting recently reported promising results in terms of local control and both acute and late toxicity. Reirradiation yielded good symptomatic relief in palliative treatment.

Brain: The brain tolerance for reirradiation depends on several factors including dose per fraction, total dose administered, overall treatment time, time interval between primary treatment and reirradiation, volume of brain irradiated, adjunctive therapies, and other factors.

- Primary: There is no standard treatment for recurrent cerebral tumors and in particular for glioma. The prognosis of recurrent brain glioma is very poor with few breakthroughs in management over the past few decades. One of the main issues in treating recurrent brain tumors is the principal decision if a definitive therapy is appropriate or just palliative care. Another issue is that the best treatment regimen. A wide variety of radiotherapy techniques are used for reirradiation including 3D-conformal RT, intensity-modulated radiotherapy (IMRT), brachytherapy, stereotactic radiosurgery with similar results. Particles are now used with the aim to reduce the risk of toxicity allowed by the specific ballistic favourable properties of the beam (protons) and radiobiological advantage (carbon ions).
- Metastases: Radiotherapy is the primary modality for the treatment of single and multiple brain metastases. Unfortunately, more than half of these patients eventually progress. Another course of radiotherapy is a viable but underutilized option. Reirradiation can resolve distressing symptoms and has shown to improve survival with minimal late neurotoxicity. Reirradiation has conventionally been done with whole brain radiotherapy, but stereotactic radiosurgery have also shown effective results.

Lung: Patients affected with intra-thoracic recurrences of primary or secondary lung malignancies after a first course of definitive radiotherapy have limited therapeutic options and they are often treated with a palliative intent. Recently, re-irradiation has raised a renowned interest in this topic with the use of stereotactic ablative radiotherapy (SABR) that has shown to be an appealing approach, due to the optimized dose distribution. Reirradiation with the use of protontherapy has been recently used in this setting; initial reports showed feasibility and good results in terms of local control. In summary, lung reirradiation is now widely proposed with the goal of loco-regional long-term control and even cure.

The Seminar was able to offer to the audience an updated state of the art of the topic of reirradiation stimulating the discussion on this debated issue and stimulating the proposal of a second event in the future.

2015 Pezcoller Foundation-ECCO Recognition for Contribution to Oncology

It is a great pleasure for the Pezcoller Foundation to report that the winner of the 2015 Pezcoller Foundation-ECCO Recognition for Contribution to Oncology has been Dr. Klaus Meier, Head of the Department for Clinical and Hospital Pharmacy in the Heidekreis-Klinikum of Soltau in Lower Saxony, Germany.
Klaus Meier studied theology with the master in 1975 and has finished as candidate studies of paedagogics and the studies of pharmacy in 1981 with the approbation from the ministry of health in Kiel.
Following is the motivation of the Award from the Selection Committee which met in August 2015:" Dr Meier has been the cornerstone and the pioneer of the oncology pharmacy in Europe. He launched in 2000 the ESOP (European Society of Oncology Pharmacy) representing about 3000 members from more than 27 countries. He was created in Germany the QUAPOS (quality standard for oncology pharmacy practice) which is now the standard in Europe. Due to its continuous efforts, in many European countries, pharmacists were now indispensable as an integrated member of the clinical oncology team. ESOP standards are now very attractive for many non-European countries, serving thus as model for implementing or updating local practices and legal guidelines. Dr Meier has been one of this small number of pharmacists which contributed around the world to demonstrate the role of pharmacists for the full benefit of our patients and to push the idea of a multi-professional approach of cancer patient care which is the plain justification of ECCO.."
Dr. Meier gave his Plenary Lecture in Vienna on September 27 during the 18th ECCO – 40th ESMO – European Cancer Congress.

Following is the article which appeared on “the 0ncopost” , the Official News ECCO-ESMO.As a member of the vast global medical research community, every oncology scientist knows they have something important to contribute. From simple cell counts to complex trials, every experimental result supports the fight against cancer. But some individuals really stand out from the crowd for their pioneering work. In yesterday’s Presidential Session III, Professor Klaus Meier, President of the European Society of Oncology Pharmacy (ESOP), received the honour he deserves: the Pezcoller Foundation-ECCO Recognition for Contribution to Oncology.

Professor Meier is a cornerstone of oncology pharmacy in Europe. In 2000, to promote the role of pharmacists in clinical oncology, he launched the ESOP; today, it represents over 3000 members from more than 27 countries.

Professor Meier also spearheaded initiative to develop and introduce the “Quality Standard for Oncology Pharmacy Practice” which has been adopted across Europe. Indeed, ESOP standards and frameworks are now used in countries all around the world.

A tireless advocate for the pharmacy community, his drive has helped to make pharmacists respected, indispensable members of clinical oncology teams across Europe.

The award – a collaboration between the European CanCer Organization and the Pezcoller Foundation which started in 1999 – recognizes an individual who has dedicated their professional life to the improvement of cancer treatment, care and research. Professor Meier was selected by an international committee appointed by the ECCO and the Pezcoller Foundation Presidents.

28th Pezcoller Symposium

Trento, Italy; June 20-21, 2016

Initial steps on the route to tumorigenesis

Co-Chairs: *David Livingston, Mariano Barbacid, Alberto Bardelli, Massimo Loda, Enrico Mihich, Stefano Piccolo, Eugenia Piddini*

Focus and Goals: This Symposium will focus on current knowledge of what molecular and biological steps must be taken for a normal cell in a given organ to acquire neoplastic potential and, eventually, full malignancy. From recent work of multiple speakers, it is clear that permission to enter a pathway to tumorigenesis requires cells to pass through multiple physiological 'gates'. The nature of these control events and how to detect whether or not future cancer cells have successfully overcome them will be prime foci of this meeting. Ideally, an ever richer and more accurate understanding of these steps could lead to rational, new approaches to molecular cancer prevention.

The final program will be available on www.pezcoller.it

2015 Begnudelli Award. From the left: President Davide Bassi, Luigi Pasini University of Trento CIBIO, Riccardo Taulli University of Turin, Eleonora Grisard University of Padua and National Cancer Institute of Aviano.

Save the date!

28th Pezcoller Symposium

June 20-21, 2016
Trento, Italy

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