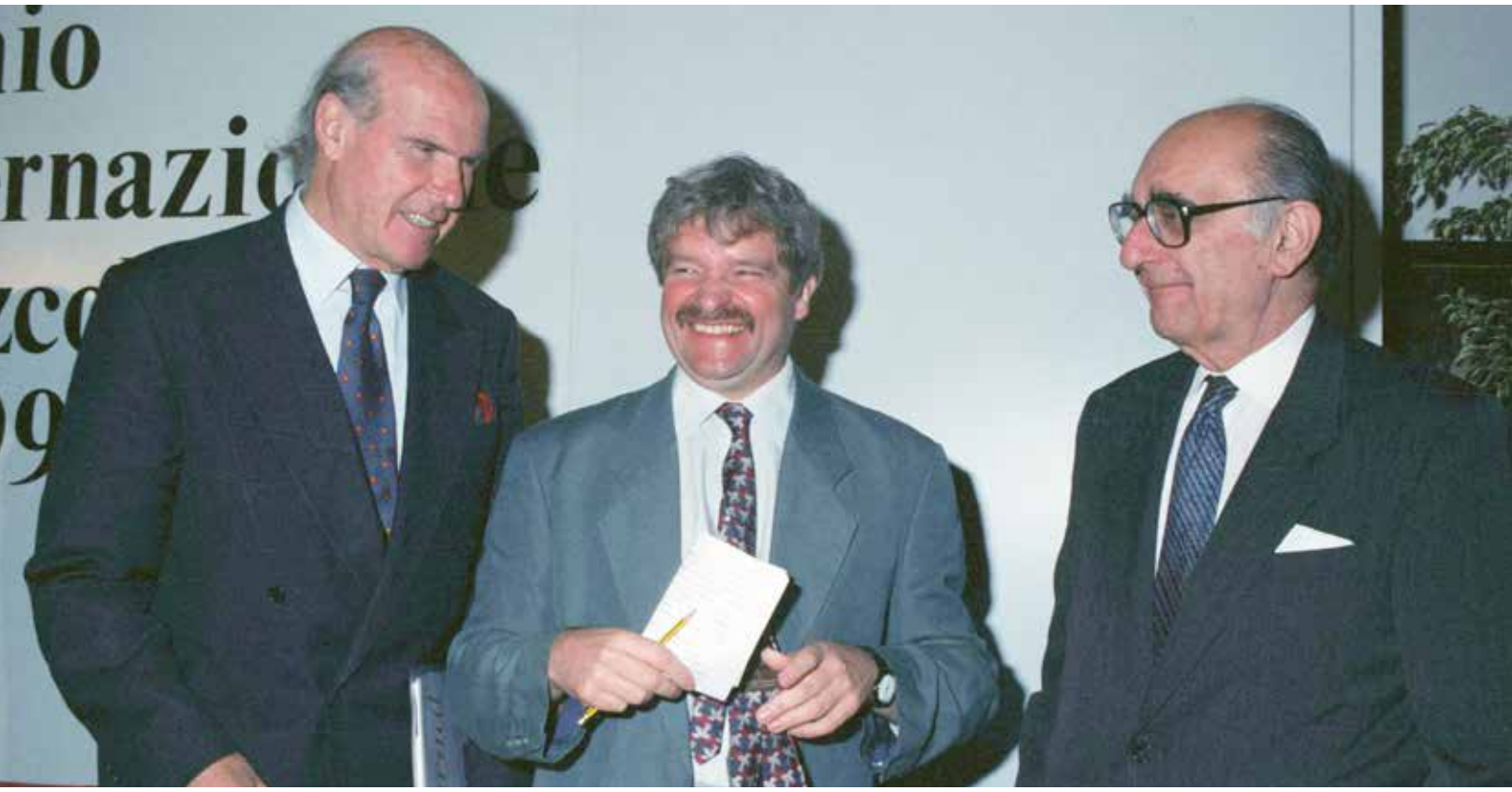
The Pezcoller Foundation

Journal



Summary

News from the
Pezcoller Foundation Word

Year 26 – no. 47
November 2016

November 2016
Editorial

I'm glad to remind that dr. Joan Massagué was the winner of the 19th Pezcoller Foundation-AACR International Award for Cancer Research for his important discoveries in TGF-ß biology, now considered fundamental to our understanding of cellular physiology. His pioneering efforts were the first to delineate the TGF-ßsignaling pathway and its mechanism of action from receptor activation to the regulation of key target genes. Furthermore Dr. Massagué's studies demonstrated how TGF-ß can be both a growth suppressor and promoter of metastasis. The day before the Award Ceremony Dr. Massagué gave a lecture at Ci.Bo, the Centre for Integrative Biology of the University of Trento, attended by students PhD and post doc and professors . In this issue we publish the article written by two researchers concerning the lecture.

I have also the opportunity to inform that the 2016 Pezcoller Symposium entitled "Initial Steps on the Route to Tumorigenesis" took place in Trento June 20-21, co-chaired by David Livingston, Mariano Barbacid, Alberto Bardelli, Massimo Loda, Stefano Piccolo, Eugenia Piddini with the participation of a significant number of outstanding speakers. They were: Mariano Barbacid, Eduard Batlle, Teresa Davoli, Glenn Dranoff, Benjamin Ebert, Manel Esteller, Matthew Freedman, Meri Huch, Juergen Knoblich, Richard Marais, Eduardo Moreno, Jorge Moscat, Sir Bruce Ponder, Reimer-Hans Rodewald, Marc van de Watering, Brian Wolpin, Omer Yilmaz.

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, recognizing the best posters, to Ester Beana from the UK Cancer Research Manchester Institute, Elisa Donato from the Italian Institute of Technology, Center for Genomic Science Milan and Fulvio Chiacchiera from the European Institute of Oncology (IEO) Milan.

On July 12, 2016 during the EACR 24 Biennial Meeting in Manchester the Pezcoller Foundation was proud to give the third PEZCOLLER FOUNDATION-EACR AWARD to Dr. Yardena Samuels of the Department of Molecular Cell Biology of The Weizmann Institute of Rehovot in Israel.

This recently constituted Award celebrates academic excellence and achievements in the field of cancer research. The award is presented biennially to an European researcher of excellence with no more than 15 years post-doctoral experience since completing their PhD (or equivalent degree). Dr. Samuels was awarded € 10.000 and gave the Pezcoller Foundation-EACR Cancer Research Award Lecture. The Pezcoller Foundation was represented by Prof. Donatella Dal Bufalo, member of the Selection Committee.

The President and The President Emeritus attended the Annual SIC Congress in Verona on September 8th where two bi-annual fellowships were given in memory of Ferruccio and Elena Bernardi and of Alice Triangi. The selection was made in cooperation with the Società Italiana di Cancerologia and two candidates were selected among 44. Dr. Annalisa Lonetti, who is doing her research at the Department of Biomedical and Neuromotor Sciences at the University of Bologna, was selected for the Ferruccio and Elena Bernardi Fellowship, while Dr. Mattia Boeri, of the IRCCS Foundation, Italian National Cancer Institute of Milan was selected for the Alice Triangi Fellowship.

In this issue we are also glad to present the next 29th Pezcoller Symposium "Building New Bridges between Basic and Cancer Science" .

Gios Bernardi
Editor and President Emeritus

Picture on front page: Umberto Veronesi, Paul Nurse Pezcoller Award in 1995 and Nobel Prize in 2001, Enrico Mihich 1995

TGF-ß signalling from cytostasis to metastasis

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Doctor Joan Massagué (Ed. the current director of the Sloan Kettering Institute, New York, NY) recently received the Pezcoller Foundation award for his lifework in cancer research. He has been dedicating his career in the elucidation of processes related to tumour biology with particular attention to the involvement of the TGF-β signalling in the disease. Dr. Massagué contributed largely to our knowledge in the field, starting from uncovering the circuit of molecules regulated by TGF-β and their link to tumour biology and lately, he focused on the mechanisms of metastasis formation trying to shed light on this important event of disease progression, still poorly understood even though recognised as one of the main causes of therapeutic failure and patient death.

With more than thirty cytokines identified to date belonging to TGF-β family, this particular pathway has been associated to a broad range of different functions in animal biology, driving embryonic development, but also homeostasis and regeneration in the adult tissues, and leading to disease conditions whenever a defect emerges.
The different roles covered by the TGF-β family are managed through an apparently simple pathway composed by transmembrane receptors that, once activated by extracellular cytokines, signal to SMAD proteins to form complexes and accumulate in the nucleus, where they modulate gene expression selectively. To quote Dr. Massagué, "…overall TGF-β in physiological processes represent a signal of constrain. It tells to go on, but not too much".
However, one of the concept that emerged very soon in the field, was the context-dependency of the TGF-β effects, so that the very same members of the TGF-β family are able to drive opposite responses depending on the cell types and conditions. Thus, TGF-β sustains embryonic stem cell state by acting on master regulators of pluripotency but also induces cell differentiation in concert to different partners, inhibits cell proliferation but also promotes cell growth, suppresses tumour growth while encouraging metastatic processes. As a consequence of the duality of TGF-β nature, the identification of the factors involved in the signalling response became one of the leading focus of research. Now we know that the main determinants of the TGF-β function are the availability of other partner transcription factors at the promoter level and the epigenetic status of the target genes. Different combinations of these determinants lead therefore to very different outcomes that have to be considered in the perspective of developing a successful therapy.

Considering primary tumours, they are highly influenced by growth factors and the microenvironment in which they form. Here TGF-β signalling has a tumour suppressor activity, inducing differentiation and cell cycle arrest of tumour progenitor cells (i.e. the cells able to proliferate in the malignancies), and also it shows the ability to induce apoptosis in both pre-malignant and malignant cells, even if with different extent.
Despite these mechanisms, by which TGF-β is depicted has a good guy in the fight against cancer, very often the tumour cells learn how to avoid this constraint signal and, as a matter of fact, TGF-β switches to a pro-metastatic entity, thus becoming the bad guy to be defeated.

As a consequence, how this switch happens became a key question for Dr. Massagué.
One possibility is the mutation of the TGF-β

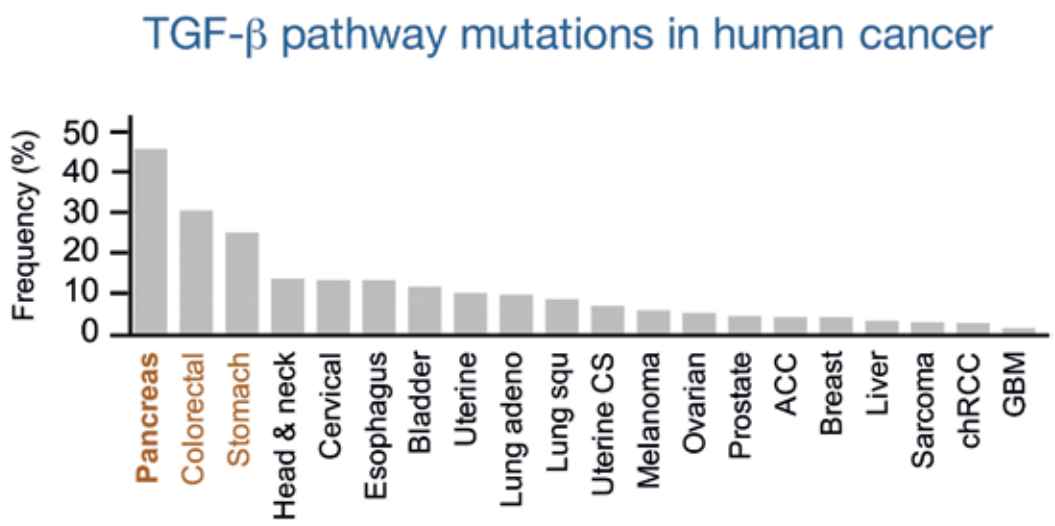

Fig 2. Frequency of TGF- ß family members mutated in human cancers.

downstream effectors (Fig 2). Usually, in the context of a KRAS mutation (the main oncogenic driver for Pancreatic Ductal Adeno-Carcinoma, PDAC), the presence of TGF-ß activates two opposite signals (i.e. Epithelial program and epithelial-to-mesenchymal transition, EMT) inducing cellular apoptosis due to this conflict (Fig 3). The absence of SMAD4 (45% of PDAC) due to either deletions or mutations, tip the balance in favour of EMT, thus preventing the apoptotic events, activating metastatic processes and tumour growth.

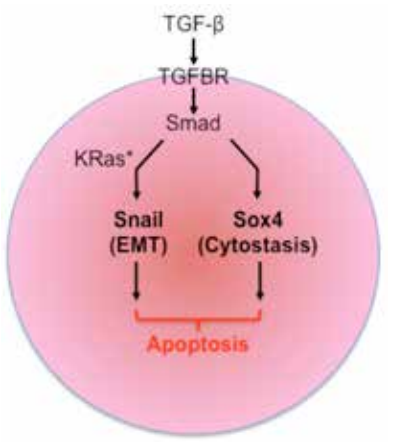

Fig 3. Conflict of the TGF-ß signalling in PDAC. Activation of the TGF-ß signalling within a KRAS mutated background activates two opposite responses: Sox4 induction stimulates cytostasis, while Snail activates the EMT program. As a results the cell undergoes apoptosis. Loss of Smad4 function prevents the conflict generated by the opposite signals resulting in tumour induction.

Another example of TGF-ß involvement in cancer was reported in colorectal cancer where, despite cells exhibit inactivation of the TGF-ß pathway, the pathology is oddly characterised by increased TGF-ß production. Here the cytokine acts on stromal cells (where the TGF-ß pathway is intact), to induce interleukine-11 production that provides a survival advantage to metastatic cells.

Various reports show dissemination and metastasis development as a dynamic process that starts quite early during tumour progression. The identification of mediators of metastases and colonisation together with a better understanding of cell heterogeneity within a tumour will put the basis for the next generation targeted-therapies for cancer, with the final aim to prevent metastasis formation rather than treat them once established.

Scientific discoveries and technical innovations during the last decades contributed extensively to the human wellbeing, improving our lifestyle and our ability to face diseases. Nevertheless, one of the most diffuse pathologies and leading cause of death worldwide remains a cloudy field, where almost no cure is available. Dr. Massagué's work highlight the influence of cellular context on TGF-ß signalling, where a little variation may change radically the outcome, forcing both researchers and clinicians to adapt to this unstable landscape.

2016 Pezcoller Foundation - EACR Cancer Researcher Award

IThe EACR and the Pezcoller Foundation are delighted to announce that the 2016 Pezcoller Foundation – EACR Cancer Researcher Award has been awarded to Professor Yardena Samuels (Department of Molecular Cell Biology and Director, Ekard Institute for Cancer Diagnosis Research, MICC, Israel).
The Samuels laboratory uses various sequencing approaches to identify the genetic changes that underlie melanoma. Once these mutations are identified, her group focuses on characterising the biochemical, functional, and clinical aspects of the most highly mutated genes.
The Pezcoller Foundation – EACR Cancer Researcher Award celebrates academic excellence and achievements in the field of cancer research. The award is presented biennially to a researcher of excellence with no more than 15 years post-doctoral experience. Professor Samuels gave the Pezcoller Foundation – EACR Cancer Researcher Award Lecture at the EACR24 Congress in Manchester, 09-12 July 2016 and received an unrestricted honorarium of €10,000.

Previous Winners
2014: Professor Eduard Batlle (IRB Barcelona, Spain)
2012: Professor Eric So (King's College London, UK)
For further details about the previous winners, visit the EACR website.

In the picture from the left: Dr. Donatella Del Bufalo (Experimental Chemotherapy Laboratory Regina Elena National Cancer Institute), Yardena Samuels, winner, Prof. Moshe Oren (Weizmann Institute of Science Rehovot Israel)

Fondazione Pezcoller - Marcello Marchi grant for young reserachers

This year the Pezcoller Foundation was able to sign an agreement with the University of Trento and to fund a three year research project to be done in the Centre for Integrative Biology.
This was possible thanks to a donation in memory of Marcello Marchi, MD in Trento who dedicated his whole life to the medicine.
Following is a brief description of the experimental context in which the researcher will work.

"Extracellular vescicles for cancer diagnosis and prognosis."
To our understanding tumor heterogeneity, even that within the same patient, is a formidable obstacle to effective therapy. This tumor feature is also a crucial factor for confounding and incomplete prediction of patient response. The development of diagnostic and of prognostic tests that can help define the clonal variation of tumor cells has the great potential to suggest specific treatments additionally increasing the overall survival; yet more effective, sensitive, and less-invasive approaches are needed.
In the last years, it has become evident that cells exchange information not only by sending out signals composed of single molecules but also by secretion of extracellular vesicles (EVs), with dimensions ranging from 50 to 1000 nm). These EVs are defined by a lipid bilayer containing a selection of proteins, lipids, and nucleic acids. The quantity of circulating EVs dramatically increases during cancer development, and it has been shown that the molecular composition of each EV mimics the parental cell or tissue. In this context, EVs from liquid biopsies (basically peripheral blood samples) can become a valid source of biomarkers for early stage diagnosis of cancer and can offer information on the biological status of tumor evolution comparing normal versus disease states.
Notably, in comparison with circulating tumor cells that were virtually exploited to profile the clonal origin of the tumor even though regarding a single cell type, EVs are easy to detect because of their abundance and can reflect the complex heterogeneity of the entire tumor, as well as its adaptations to therapy. Newly developed instruments are now introduced to characterize circulating EVs obtained from biofluids in a non-invasive ways, including serum, plasma, saliva, urine, amniotic fluid, breast milk. Some recent explorative studies demonstrated the presence in EVs of potential nucleic acid-based markers. Improvement of isolation methods from liquid biopsies, including the possibility to obtain uniformly sized vesicles, would allow acquiring better insights on composition and quality of EVs. These advancements are expected to pave the way for the discovery of novel tumor biomarkers, and to render EVs from liquid biopsies in cancer patients an important foundational asset for Precision Medicine.

In memory of Umberto Veronesi

The present issue of the Pezcoller Journal is published after the death of Professor Umberto Veronesi.

Prof. Veronesi has been a good friend of the Pezcoller Foundation. For this reason, I would like to remember the first years of this relationship.
After the establishment of the first board of directors (1986) the Pezcoller Foundation needed to find an outstanding scientist to put together and guide an international selection committee, able to choose the candidate for its important international award. As a matter of fact, this objective turned out to be a daunting task for the peripheral location (not only in geographic terms) of Trento. Umberto Veronesi understood the ambitious goals of this enterprise, and acknowledged the inspiring personality of Alessio Pezcoller and agreed to create the first scientific selection committee with the organizational support of the European School of Oncology Milan.
Umberto Veronesi then chaired the international committee which selected the first winner Vincent De Vita in 1988 and afterwards Tubiana, Vogelstein and Nurse.

After the subsequent agreement with the AACR, which changed the denomination of the award into Pezcoller Foundation-AACR International Award for Cancer Research, Prof. Veronesi continued to be a good friend of our Foundation.

Prof. Alessio Pezcoller greets Prof. Umberto Veronesi at the second Pezcoller Award for Cancer Research in 1991

In the meantime, he had become Director of the National Institute of Tumors, he had founded IEO (the European Institute of Oncology), and the Veronesi Foundation. He had also organized the important annual World Conferences on the Future of Science in Venice and afterwards the annual International Conferences "Science for Peace". He also became Health Minister of the Italian government. He always maintained his friendship with the Pezcoller Foundation. The Pezcoller Foundation would like to express its deepest sympathy to the family, the international world of science, the Italian scientific community and all the people who have been cured by his capability and human understanding.

We are pleased to propose hereafter an interview to Prof. Veronesi, when he attended the first Pezcoller Foundation Award in Trento.

INTERVIEW WITH PROF. VERONESI

Q. Professor Veronesi, could you please describe for us Prof.Pezcoller?

A. He is an extraordinary person, a man who has dedicated his whole life to patients and also to science. A stern and honest man fully dedicated to the cause of medicine and the progress of humankind.
At the end of his long career as a surgeon, part of which actually spent in a university hospital directed by the great Milan-based surgeon Prof. Donati, Alessio Pezcoller decided to put into this Award all he had achieved and collected during his life, both in material and moral terms.
As he himself stated, this Award is aimed at putting a price on the head of a killer, that is to promote a movement so that this killer, i.e. cancer, may be one day eliminated.

Q. What is the role of this Award in the wider international context of health-related awards?

A. It is one of the great international awards. There are not many of them. Of course, we should mention the world-famous Nobel Prize, and then the General Motors Prize in the United States, and the Pezcoller Award in Italy. These are the three most important prizes for medical sciences that I am aware of.

Q. Whom do you normally award with the Pezcoller Award?

A. This is a difficult question to answer. Every time there is a lot of discussion, because, indeed, as the Pezcoller Award is very renown, there are many qualified candidates. Therefore, one has to make difficult choices, because on one hand we would like to reward great and original research-related projects and their outcomes, but on the other hand, we want to acknowledge also the impact that these ideas have had on the clinical practice. In other words, we would like to give priority to those research projects and ideas that have had a real impact on the development of therapies or diagnostic methods.

29th Pezcoller Symposium Focus and Goal

Trento, Italy, June 22-23, 2017

Building New Bridges between Basic and Cancer Science

Co-Chairs: *David Livingston, Alberto Bardelli, Massimo Loda, Stefano Piccolo*

Focus and Goals: The 2017 Pezcoller Symposium will focus on a growing set of observations in the cancer field and their implications for the future.
The past decade has witnessed the development and application of groundbreaking technologies that have improved cancer diagnosis, prognosis making, and therapy. As a result, the outlook for cancer patients has brightened. Chief among these new approaches are a strong and productive thrust towards the discovery and development of powerful targeted agents for cancer therapy; the discovery and development of novel, immunologically-directed therapies that have led to extraordinarily positive therapeutic effects in certain cancer patients; and the growing value of deciphering the sequences of cancer genomes and its contribution to the design of more precise and, hence, effective therapy for individual patients.
These major advances, notwithstanding, cure still remains elusive, especially for advanced and particularly aggressive cancers. One major reason is that the basic scientific forces that drive cancer development, establish its aggressive and sometimes lethal nature, and wall it off from immunological killing remain incompletely or poorly understood. Thus, without the growth of new, basic cancer science knowledge, frequent cures of most advanced or aggressive cancers will be difficult to achieve. Hence, this Symposium aims to define the limits of our understanding of the basic biology of cancer cells and of the cells of the tumor microenvironment in which cancers arise and proliferate. It will also propose and describe new opportunities for moving beyond these limits. In essence, this meeting has been built upon the premise that ongoing progress in these endeavors will be needed to achieve ever better cancer therapy and prevention.

2016 Begnudelli Award - 28th Symposium Best Poster. From the left: President Davide Bassi, Fulvio Chiacchiera from the European Institute of Oncology of Milan, Ester Beana from the Prostate Oncobiology Laboratory of the Cancer Research UK Manchester Institute, Elisa Donato from the Italian Institute of Technology Centre for Genomic Science of Milan.

Save the date!

29th Pezcoller Symposium

June 22-23, 2017
Trento, Italy

Building New Bridges between Basic and Cancer Science

The Pezcoller Foundation

Journal

Six-monthly review of the
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Proprietario/editore:
Fondazione Prof. Alessio Pezcoller - Trento
n. 36 - Registro delle Persone Giuridiche
presso il Commissario del Governo
della Provincia di Trento
Redazione: Via Dordi 8 - 38122 Trento
Direttore Responsabile: Gios Bernardi

"The Pezcoller Foundation Journal"
year 26, n. 47, Semestrale novembre 2016
Poste Italiane spa
Spedizione in abbonamento postale
D.L. 353/2003 (conv. In L. 27/02/2004 n. 46)
Art. 1, comma 2, CNS Trento
taxe percue / tassa riscossa