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# Journal

Summary




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Editorial

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*We are grateful to Dr. Pier Paolo Pandolfi for his kindness to let us publish the lecture entitled "The ceRNA code: A new theory on how RNAs communicate and its implication for biomedical research", given in Padua at VIMM on May 4, before the Award ceremony in Trento.*
*We are glad to remind you that Pier Paolo Pandolfi is the prestigious recipient of the 2011 Pezcoller Foundation-AACR International Award for Cancer Research.*

*We like to remind that the annual Stanley J. Korsmeyer Lectureship has been started by the Pezcoller Foundation in 2006 in accordance with the AACR American Association for Cancer Research and the VIMM, Venetian Institute of Molecular Medicine in Padua (Italy). The goal of this event is to honour the fundamental contribution of the late S. Korsmeyer, an international outstanding leader in cancer biology, whose pioneering observations opened the molecular era of programmed cell death.*
*S. Korsmeyer was the recipient of the Pezcoller Foundation-AACR International Award for Cancer Research in 2004. Although under heavy treatment for loans cancer, he presented his last European lecture by the VIMM immediately before receiving the Pezcoller Award. Unluckily he passed away a few months later. Therefore we wish to remember Stanley Korsmeyer every year with this lecture given by the recipient of this Award.*

*We are also presenting on the last pages the call for the 2012 Pezcoller Foundation-AACR Award for Cancer research.*

*The 2011 Symposium entitled "Engineering in Cancer Research" took place in Trento last June and was very successful for the high level of the five sessions and for the large participation. As usual we gave also the "Pezcoller Begnudelli Awards" for the best posters to three deserving researchers: Luca Vannucci, University of Praga, Czech Republic; Andrea Palamidessi of IFOM-FIRC, Milan, Italy and Georges Said, University of Reims, France. We are also glad to present the next 24th Pezcoller Symposium which will be held in Trento on June 14-16, 2012 and will be entitled "Cancer escape from therapy".*

*Gios Bernardi MD*
*Editor and Pezcoller Foundation President*

Picture on front page:
2011 Pezcoller Foundation – AACR Award for Cancer Research, Trento May 6 2011.
From the left: Gios Bernardi, President of Pezcoller Foundation, Pier Paolo Pandolfi, recipient of the Award, Margaret Foti CEO of AACR

# The ceRNA code: A new theory on how RNAs communicate and its implication for biomedical research

*Pier Paolo Pandolfi*

*Cancer Genetics Program, Beth Israel Deaconess Cancer Center, Departments of Medicine and Pathology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA 02215, USA.*

*Preamble*

For several decades the term 'gene' has been synonymous with regions of the genome encoding mRNAs that are translated into protein. However, recent studies utilizing the latest genome sequencing technologies are telling us that the effective functional genomic information goes far beyond the coding genes. Indeed, only approximately 2% of the genome is coding for protein, whereas it is becoming clear that approximately 50% of the genome is transcribed into RNA material and that the information carrying capacity of the genome is much more vast, extending beyond the protein coding genome. The emergence of this exciting genomic and transcribed "space" begs in turn two critical questions that cancer biologists and oncologists, but also biomedical investigators at large, must consider in the post-genomic era: 1) Are we are studying the relevant molecular spaces that can lead to cancer and other diseases? 2) Are we drugging the most effective targets to treat cancer and other diseases?

*The Non-Coding Revolution*

Some lower organisms have been identified to have comparable numbers of protein-coding genes when measured up to humans (Baltimore, 2001). Such a small numerical difference in coding genes is not sufficient to explain the diversity of cell types and tissues found in complex organisms. The fact that the human genome is approximately 30 times larger than that of *C. elegans* suggests that the non-coding portion of the genome is of crucial importance in dictating the greater complexity of higher eukaryotes. Indeed, the developmental complexity of organisms is more closely related to the amount of non-coding sequences in genomes, suggesting that they harbor critical regulatory information (Costa, 2008; Mattick, 2009).
Studies characterizing the transcriptome have revealed that most of the mammalian transcriptome does not correspond to annotated exons of protein-coding genes (Kapranov et al., 2007). This implies that the fraction of the mammalian genome that is used as "information messenger" is much greater than previously predicted. Indeed, systematic analyses of the genome and transcriptome in disease and cancer have revealed profound alterations in the non-coding genome (Beroukhim et al., 2010; Futreal et al., 2004; Stratton et al., 2009). In cancer in particular, rearrangements such as deletion, amplification, inversion and chromosomal translocation can lead to aberrant expression of coding transcripts as well as non-coding transcripts.
If however this is the case, if this new genetic dimension is important in physiology and disease pathogenesis, we are currently confronted by the seemingly insurmountable challenge that such vast genetic space can be solely regarded as such as dark matter in need of functional annotation. Critically, we

do not have at hand any systematic approach to deconvolute such a huge library of cryptic information. There is no universal RNA code to apply towards this end: we have no language to read.

*The ceRNA essentials*

Despite the association of a small subset of lncRNA with specific regulatory mechanisms, thus far there have been no attempts to attribute a general function to non-coding transcripts, because a language comparable to the triplet-codon amino acid code was missing. Today I describe the ceRNA hypothesis, its components, the consequences of altering ceRNA homeostasis and studies supporting our current knowledge on ceRNAs:

1. The microRNAs
MicroRNAs are short RNA molecules of approximately 22 nucleotides in length that bind to partially complementary sequences on target RNA transcripts, usually resulting in repression of target gene expression (Bartel and Chen, 2004). Over the past decade, the catalogue of microRNAs in a number of organisms has steadily grown, with the human genome now predicted to encode several thousand microRNAs, over a thousand of which have been confirmed experimentally (Thomas et al., 2010). microRNAs are generated from longer precursor RNA species by several different pathways involving the RNAse III type endonucleases DROSHA and DICER (Thomas et al., 2010). Mature microRNAs are loaded into a multi-protein complex termed the microRNA-induced silencing complex (miRISC), which is guided to repress target transcripts. The precise biochemical rules that define targets remain the subject of intense study; however, it is clear that both partial Watson-Crick complementarity as well as local secondary structure within the target RNA play important roles (Bartel, 2009). microRNAs bind preferentially, but not exclusively to the 3'UTR of their targets through recognition of sequences referred to as microRNA recognition elements (MREs) (Thomas et al., 2010). microRNAs can function in a combinatorial manner if mRNA transcripts harbor numerous MREs for more that one microRNA. Furthermore, since each microRNA may repress up to hundreds of mRNAs (and ncRNAs see below), the mammalian transcriptome is without a doubt regulated in this manner (Friedman et al., 2009; Thomas et al., 2010)}. In fact, aberrant expression of microRNAs has already been implicated in numerous disease states, and microRNA-based therapies are currently under investigation (Ventura and Jacks, 2009). MicroRNA numbers are finite, such that we can catalogue them and consider the corresponding MREs as letters of a large alphabet in a language used by ceRNAs to communicate with one another.

2. The coding genes
In the human genome, approximately 20,000 protein-coding genes have been identified (Baltimore, 2001). Ultimately, the proteins encoded by these genes make up all the building blocks of cells and organisms. mRNA sequences of coding genes are often densely covered in MREs, which explains how their expression is regulated through microRNAs (Friedman et al., 2009). Our increasing capacity to identify MREs lining coding gene transcripts allows us to predict the extent of microRNA-dependent regulation. This predictability, coupled with appropriate validation steps, will prove to be critical in understanding the ceRNA hypothesis.

3. Pseudogenes
A pseudogene is a genomic locus that resembles a known gene, yet has been previously defined as "non-functional", "junk" or an "evolutionary relic". They were typically considered inconsequential because, with few exceptions, they contain premature stop codons, deletions/insertions and frameshift mutations, which prevent them from encoding fully functional proteins (Adra et al., 1988; Betran et al., 2002; Soares et al., 1985). Human genome sequencing efforts have revealed the existence of approximately 19,000 pseudogenes, many of which are expressed as RNA transcripts. Pseudogene sequences are often well conserved, suggesting that selective pressure to maintain these genetic elements exists, and that they may indeed play an important role in cellular homeostasis (Pink et al., 2011).
Pseudogenes exist as non-processed or processed genetic elements. Non-processed pseudogenes result from genetic duplication of their respective ancestral genes, thus retaining introns as well as upstream and downstream regulatory elements (D'Errico

et al., 2004). Processed pseudogenes are produced through an mRNA retrotransposition mechanism and do not contain introns. Despite lacking canonical promoters, processed pseudogenes utilize other proximal regulatory elements for transcription (Birney et al., 2007). In fact, transcription of pseudogenes has been demonstrated to display tissue-specificity, and to be activated or silenced in specific pathological conditions, such as cancer (Bristow et al., 1993; Dahl et al., 1990; Dubbink et al., 1998; Olsen and Schechter, 1999; Suo et al., 2005; Zhang et al., 2006). This indicates that pseudogenes may play a role in carcinogenesis, although the mechanisms through which this would occur remain elusive. Importantly, the high conservation of sequence in turn implies that expressed pseudogene RNAs will be targeted by the same microRNAs that target their ancestral cognate genes (Poliseno et al., 2010).

4. Long non-coding RNAs (lncRNAs)

LncRNAs are typically 300 to thousands of nucleotides in length. The precise number of lncRNAs is expanding as they are being further characterized, approximating to date the 10,000 genetic units, nevertheless little is known about their cellular functions. Of the few lncRNAs that have been characterized, a small subset have been linked to epigenetic mechanisms, as exemplified by *XIST*, which is implicated in X-chromosome inactivation (Brown et al., 1992). LncRNAs are also implicated in the process of transcriptional initiation in eukaryotes (Resch et al., 2008). Recently, a new group of evolutionary conserved lncRNAs were identified and named large intergenic non-coding RNAs (lincRNAs) (Guttman et al., 2009; Khalil et al., 2009). A subset of these lincRNAs are reported to be associated with epigenetic modifications through interactions with proteins that can bind and associate with DNA, such as histones and polycomb proteins (Khalil et al., 2009). Some others have been shown to act at the transcriptional (Huarte et al., 2010) or post-transcriptional (Gong and Maquat, 2011) level. Similar to coding genes and pseudogenes, ncRNA transcripts are densely populated with MREs, as such they are also subjected to microRNA regulation (Zhao et al., 2008). Moreover, the estimation that lncRNAs may match or even exceed protein-coding mRNAs in number highlights the potential importance of being able to predict their cellular functions.

*The hypothesis explained: the ceRNA language*

microRNAs are negative regulators of gene expression through binding to specific MRE sequences and, consequently, decreasing the stability of target RNAs and/or limiting their translation (Fabian et al., 2010). Accordingly, microRNAs are commonly viewed as active regulatory elements, while the target mRNAs are viewed as passive targets of repression. By contrast, we propose that, in addition to the conventional microRNA à RNA function, a flipped RNA à microRNA function exists, where RNAs can regulate each other through their ability to compete for microRNA binding. In other words, target RNAs can sequester microRNAs, thereby protecting other target RNAs from downregulation by the sequestered microRNAs. In this framework, we propose MREs as the letters of the "RNA code", like triplets are the letters of the "protein code".

The ceRNA hypothesis revisits a fundamental rule of biology articulated by Francis Crick whereby a gene has to be encoded into mRNA and translated into a protein to exert its function (Crick, 1970). While Crick's theory absolutely holds true, it does need to be integrated given the discovery of numerous functional ncRNAs. We propose here that protein-coding mRNAs may possess a second independent and genetically encrypted function through their ability to regulate other RNAs. An intriguing repercussion of this hypothesis entails that the non-coding function of a mRNA may sometimes be consistent with the coding function, yet other examples where the two functions are incoherent or even opposite may also exist, thereby creating built-in regulatory loops, functional complexity and diversification. Furthermore, the ceRNA hypothesis confers a new function to 3'UTRs. Beyond acting as *cis* regulatory elements that impact the stability of their own transcripts, they are now unveiled as *trans* modulators of gene expression through microRNA binding.

In addition, since not only mRNAs, but any cellular RNA molecule can act as a ceRNA, our hypothesis attributes a novel biological function to the transcriptome as a whole and allows to identify gene networks never previously contemplated (Poliseno et al., 2010). Specifically, in a recent publication from our group, we have demonstrated the ability of a pseudogene transcript to bind

to and compete for the same collection of microRNAs as its ancestral gene. We investigated the interaction of the RNAs encoding the PTEN tumor suppressor gene and its closely related pseudogene, *PTENP1* (Poliseno et al., 2010). We identified that MREs for several microRNAs that target the 3′UTR of *PTEN* are conserved in the *PTENP1* RNA sequence. Overexpression of the *PTENP1* 3′ UTR led to increased levels of *PTEN* transcripts and protein and to growth inhibition in a *DICER*-dependent manner. Focal copy number losses at the *PTENP1* locus in samples from patients with sporadic colon cancer suggest that *PTENP1* could be considered a tumor suppressor gene and that there might be selection for loss of *PTENP1* during tumorigenesis (Poliseno et al. 2010). We extended this analysis to other gene: pseudogene partners (e.g. *KRAS* and its pseudogene *KRAS1P*). We and others also attributed specific ceRNA function to the 3'UTR of protein-coding mRNAs (eg. *PTEN* 3'UTR (Poliseno et al., 2010), versican 3'UTR (Lee et al., 2010 ; Lee et al., 2009), CD44 3'UTR (Jeyapalan et al., 2010)). Overall, these findings suggest that 3'UTRs from both pseudogenes and coding genes posses powerful biological activity through their ability to act as endogenous decoys for microRNAs (Poliseno et al., 2010).

*ceRNAs in disease etiology*

An important contribution of the ceRNA hypothesis lies in the principle that any RNA molecule that is expressed and possesses at least one MRE can act as a ceRNA. This is irrespective on whether it has a characterized coding function, but instead because it can compete with other ceRNAs for the binding of a particular microRNA. Indeed, the ability to identify MREs within RNA molecules will permit the elucidation of ceRNA networks and molecular interactions that would have never been identified through proteomic or conventional genomic methods. In this framework, aberrant expression of coding and non-coding (e.g. due to genetic losses or gains) as well as aberrant splicing and genetic read-through errors should be systematically studied the context of human disease. Thus we can hypothesize the role of vast numbers of uncharacterized genes into the realm of biomedical research:

Pseudogenes, are a compelling example because, they can act as "perfect ceRNAs" since they are likely to posses many of the same MREs that are harbored on their ancestral genes. However, the ability of pseudogenes to regulate the biology of a cell goes beyond the modulation of the levels of their ancestral genes. For instance, we found that the PTEN pseudogene is biologically active even in a *PTEN* null context by altering the microRNA network that is normally regulating PTEN (Poliseno et al., 2010). Moreover, since a single gene often has numerous differentially regulated pseudogenes (*e.g. OCT4*, *NPM1* and ribosomal protein pseudogenes (Balasubramanian et al., 2009)), such networks can become intricately dynamic.

Notably, our 20,000 protein-coding genes may act as ceRNAs through a function which has remained elusive in part due to our conventional experimental techniques which normally neglect UTRs and limit our functional studies to gene coding regions only. Furthermore, since binding sites for microRNAs are also located in coding regions and 5'UTRs (Tay et al., 2008), the entire transcript, and not only the 3'UTR may possess the inherent *trans* decoy function of ceRNA.

Interestingly, it has been proposed that intronic RNAs which are generated during the splicing process, may have a biological function if long lived. Since spliced RNA sequences are indeed present in cells, it follows that they have the potential to behave as ceRNAs, especially for those microRNAs present in the nucleus. Additionally, it was recently reported that a large number of 3'UTRs are expressed as RNA transcripts independently of their associated coding genes (Mercer et al., 2010). This phenomena further supports our hypothesis that 3'UTRs possess *trans*-acting biological activity.

In addition to our report on pseudogenes and 3'UTR functions in tumorigenesis, further examples of ceRNA networks have been reported. Indeed, a recent compelling study has demonstrated how *Herpesvirus saimiri* (HVS) utilizes non-coding ceRNAs in a process to downregulate host genes through sequestration of microRNAs (Cazalla et al., 2010). Such a viral mechanism may manipulate host gene expression to create a permissive cellular environment for optimal viral transformation and thereby propagate

viral disease. This in turn opens important avenues for therapeutic modalities aimed at perturbing viral ceRNA activity in infectious disease.

*ceRNAs and cancer*

A straightforward implication for cancer that stems from our hypothesis is that pseudogenes and lncRNAs should now be systematically studied as potential tumor suppressors and oncogenes.
Gross genomic losses and amplifications commonly observed in cancer could have potentially dramatic consequences for the ceRNAs contained in those regions. Moreover, gene loss events should be clearly distinguished from point mutations. In the context of the ceRNA hypothesis, gene loss will abrogate both the protein and ceRNA function, whereas point mutations leading to protein truncation will likely not affect the expression of the mRNA and thus retain ceRNA function, unless an important MRE is also affected by the point mutation. Similarly, when generating mouse models, one must consider the repercussions of knocking out and overexpressing ceRNAs. For instance, when generating knockout mice, one must consider whether only the transcript or also the protein expression is disrupted. Also when generating transgenic mice, it has been standard to only overexpress coding sequences, and not UTRs. Thus, we have neglected the full function of a gene, which we now know emanates from both the protein and the transcript, independently.
Chromosomal translocation events such as the t(15;17) translocation of APL which generates *PML-RARa* and *RARa-PML* fusion transcripts (or recurrent "readthrough" transcripts in melanoma such as *CDK2-RAB5B* (Berger et al.; Scaglioni and Pandolfi, 2007)) should be now analyzed as UTR-swaps leading to aberrant ceRNA activity. Such translocations place MRE containing transcripts under the control of non-native promoters such that their levels in the cell will be altered. ceRNA perturbation could also occur as a consequence of somatic genomic rearrangements affecting non-coding regions, which are emerging as grossly unappreciated events in many cancers (Stephens et al., 2009)
Aberrant alternative splicing events can also introduce new RNA sequences and potentially new MREs into the cell. Since splicing can be regulated or perturbed in disease and cancer (Venables et al., 2009), the associated perturbation of the ceRNA network may also have consequences. Similarly the shortening of 3'UTRs as observed in human cancer cells (Mayr and Bartel, 2009) would not solely affect microRNA-dependent mRNA regulation, but on the flipside, also alter the "ceRNA" capacity of a given mRNA transcript.
All these described events have a single feature in common; that is they represent perturbations in the expression levels of a given transcript (and consequentially MREs), irrespective of whether or not the transcript is translated into a protein. The elevated or depressed levels of the given transcript could exert oncogenic activities through an aberrant ceRNA activity.

*Open questions*

The ceRNA hypothesis relies on the knowledge of the exact number and location of MREs along RNA molecules. Although we can define numerous MREs, "the letters" of the RNA code that are "written" on each RNA species, in the near future we expect that both target prediction algorithms, whose false discovery rate is progressively decreasing, and the recently developed techniques that allow to identify RISC-associated MREs (Ago associated, followed by high throughput sequencing upon crosslinking and immunoprecipitation), will contribute significantly to the definition of the RNA code (Thomas et al., 2010).
Given that the notion of ceRNAs is still in its infancy, there is currently limited experimental evidence to outline the cellular conditions necessary for effective competition of endogenous microRNAs. Nonetheless, at this time we assume that a number of conditions must exist for ceRNA function: First, the ceRNA mechanism will depend on the relative concentration of the RNA species that sequester and of the microRNAs that are sequestered. The expression levels of the RNA species acting as ceRNA will need to be perturbed to an extent that it can either overcome or at least relieve the microRNA repression on competing ceRNAs. This would for example be the case of mRNA transcripts switched on or off at the transcriptional level in different developmental stages or physiological/pathological conditions, because

their concentration within the cell can vary by several orders of magnitude. Similarly, the expression levels of the sequestered microRNAs must not exceed specific thresholds, since both their complete absence and their gross overexpression will abolish any competition.
Second, the effectiveness as ceRNAs will not be equal for all RNA species, but will depend on: the type, number and efficiency of MREs that they contain; their accessibility to microRNA molecules, which can be favored or impaired by their subcellular localization and by RNA binding proteins (Agami, 2010); on the cell context where they are expressed, because not all the microRNAs for which they contain MREs are present everywhere and at every time (Kosik, 2009).
Third, not all the RNAs that share MREs with a given ceRNA will be decoyed. microRNAs are predicted to target tens to hundreds RNAs, but they do not exert the same degree of repression on all of them: the primary targets are usually few, while the renmainder are just finely tuned (Bartel and Chen, 2004). It is conceivable that, when a given microRNA is sequestered by a ceRNA, only the primary targets of that microRNA will be affected.
Fourth, although a network can be built around a single microRNA, we hypothesize that the most robust ceRNA networks will be composed of transcripts that share multiple MREs. In such networks, the perturbation of a single ceRNA will have repercussions for multiple microRNAs, and thus on multiple ceRNAs belonging to the network. The identification of microRNA targets is constantly improving, and with this progress we will be better able to identify the genes making up ceRNA networks. ceRNA networks will depend on the identity, concentration and subcellular distribution of the RNA and the microRNA species that are present in a given cell type at a given moment. A further challenge will be trying to understand why such regulatory networks exist, how they may have evolved and which are the consequences of their perturbation.
In conclusion, we propose that the existence of ceRNA and the expansive ceRNA networks could provide the answers to many evolutionary questions, as they may, in part explain the correlation of genome size and organism complexity. Moreover, perturbations of ceRNA and ceRNA networks could have consequences for disease, but on the flip side, may explain disease processes and present opportunities for new therapies. Although the understanding of this field and its consequences are in their infancy, the technology is such that we are beginning to decipher the ceRNA code. As the capability to identify microRNA targets increases, we will certainly have a better grasp of ceRNA and the identity of ceRNA networks and we will be able to fully decipher the ceRNA language.

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## 2012 Pezcoller Symposium

# Cancer escape from Therapy
# 14-16 June 2012, Trento, Italy

On June 14-16, 2012, the Pezcoller Foundation will hold its annual cancer science symposium in Trento, Italy. The topic will be Cancer Escape from Therapy, and the focus of the meeting will be the mechanisms of resistance to new tumour target therapies. The Symposium will be opened by the keynote address of Prof. J. Engelman, MGH. The meeting is being co-organized by William Seller (UK), Richard Marais (UK), David Livingston (Dana Farber Cancer Institute) and with the collaboration of Enrico Mihich (Dana Farber Cancer Institute). There will be 22 speakers divided in five sessions: A) the genetics of this phenotype; B) cooption of specific signal transduction events resulting in drug resistance; C) advanced approaches to screening for various forms of resistance; D) non-tumor cell directed resistance processes; E) clinical advances in overcoming resistance.

As in the previous years, speakers give approximately 25 minute talks followed by a similar amount of time for audience discussion. These meetings have regularly provided a fertile climate for highly revealing and stimulating scientific discussion on topics of extraordinary interest in cancer science.

## Pezcoller Foundation-AACR

# Call for 2013 Pezcoller Foundation-AACR International Award for Cancer Research

The prestigious Pezcoller Foundation-AACR International Award for Cancer Research was established in 1997 to annually recognize a scientist:

- who has made a major scientific discovery in basic cancer research or who has made significant contributions to translational cancer research;
- who continues to be active in cancer research and has a record of recent, noteworthy publications;
- whose ongoing work holds promise for continued substantive contributions to progress in the field of cancer.

The Award is intended to honor an individual scientist. However, more than one scientist may be co-nominated and selected to share the Award when their investigations are closely related in subject matter and have resulted in work that is worthy of the Award. In the rare event that there are dual winners of the Award, the cash award will be shared equally between them, and the AACR Executive Committee will determine which of the two co-recipients will present the Pezcoller-AACR Award Lecture at the AACR Annual Meeting.

Candidates for the Award will be considered by a prestigious international Selection Committee of renowned cancer leaders appointed by the President of the AACR and the Council of the Pezcoller Foundation. The Committee will consider all nominations as they have been submitted; the Committee may not combine submitted nominations, add a new candidate to a submitted nomination, or otherwise make alterations to the submitted nominations. After careful deliberations by the Committee, its recommendations will be forwarded to the Executive Committee of the AACR and the Council of the Pezcoller Foundation for final consideration and determination.

Selection of the Award winner will be made on the basis of the candidate's scientific accomplishments. No regard will be given to race, gender, nationality, or religious or political view.

The Pezcoller Foundation was established in 1980 by Professor Alessio Pezcoller, a dedicated Italian surgeon who made important contributions to medicine during his career and who, through his foresight, vision and generous gift in support of the formation of the Foundation, stimulated others to make significant advances in cancer research. Previously the Pezcoller Foundation, gave a major biennial award for outstanding contributions to cancer and cancer-related biomedical science, in collaboration with the ESO-European School of Oncology.

The American Association for Cancer Research (AACR) was founded in 1907 by eleven physicians and scientists dedicated to the conquest of cancer and now has over 25,000 laboratory, translational, clinical and epidemiological scientists engaged in all areas of cancer research in the United States and in more than 60 other countries around the world. The AACR is dedicated to its mission of

preventing and curing cancer through the communication of important scientific results in a variety of forums including publications, meetings and training and educational programs. Because of the commitment of the Pezcoller Foundation and the AACR to scientific excellence in cancer research, these organizations are now collaborating annually on the presentation of the Award. This will strengthen international collaborations and will be a catalyst for advancements in cancer research internationally.
The winner of the Pezcoller Foundation-AACR International Award for Cancer Research will give an award lecture during the AACR Annual Meeting (April 2013), and the memorial Korsmeyer lecture at the VIMM in Padua and will receive the award in a ceremony at the Foundation's headquarters in Trento, Italy (May, 2013). The award consists of a prize of € 75.000 and a commemorative plaque.
**Nomination Deadline: September, 2012**

Questions about the nomination process: Monique P. Eversley, Senior Coordinator, Scientific Awards - American Association for Cancer Research, 17th Floor, 615 Chestnut Street, Philadelphia, PA 19106-4404 - Tel. +1 (267) 646-0576; E.mail: eversley@aacr.org - www.aacr.org

*Save the date!*

# 24th Pezcoller Symposium

June 14-16, 2012
Trento, Italy

# Cancer Escape from Therapy

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The Pezcoller Foundation

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Via Dordi 8 - 38122 Trento - Italy
Tel. (39) 0461 980250
Fax (39) 0461 980350
e-mail: pezcoller@pezcoller.it
www.pezcoller.it

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