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Editorial: October 2006

It is a pleasure and a privilege to reprint in this issue the first "Korsmeyer Lecture".
The annual Stanley J. Korsmeyer Lectureship has been created in accordance with the AACR American Association for Cancer Research and the VIMM Venetian Institute of Molecular Medicine in Padua to honour the fundamental contribution of the late Dr. Korsmeyer, an international leader in the field of cancer biology, whose pioneering observations opened the molecular era of programmed cell death.
Dr. Korsmeyer was the recipient of the Pezcoller Foundation-AACR International Award for Cancer Research in 2004. In the same time he presented his last European lecture by the VIMM in Padua (Italy) before his untimely death from cancer in 2005.
Therefore we wish to remember Dr. Korsmeyer every year with this lecture at the VIMM by the recipient of the Award just before the award ceremony in Trento.

Dr. Tadatsugu Taniguchi, the prestigious recipient of the 2006 Pezcoller Foundation-AACR International Award for Cancer Research, gently allows us to publish the Korsmeyer Lecture he gave at the VIMM in Padua last May. And we are very grateful for that.

In this issue we are also presenting in the back the call for the Pezcoller Foundation-FECS Recognition for Contribution to Oncology Award together with the first program of the next 19th Pezcoller Symposium on "Hypothesis driven clinical investigation in cancer".

The winners of the 2006 'Pezcoller-Begnudelli Fellowship' with Dr. R. Weinberg, Dr. G. Bernardi and Dr. E. Mihich.

In the last edition of the symposium we were glad to give the 'Pezcoller Begnudelli Fellowship' for the best posters to 3 young researchers: Roderik M. Kortlever, Netherlands Cancer Institute, Amsterdam; Yan Monnier, Cancer Centre of Lausanne; Laura Rosanò, Regina Elena Cancer Institute, Roma. (See picture).

Gios Bernardi M.D.
The Pezcoller Foundation President
and Editor of the Journal

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The Stanley J. Korsmeyer Memorial Lecture

25 YEARS AFTER THE DAWN OF CYTOKINE MOLECULAR BIOLOGY: ROLES OF IRF FAMILY TRANSCRIPTION FACTORS IN ONCOGENESIS AND IMMUNITY

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Preface

It was my special honor to deliver the first Stanley J. Korsmeyer Memorial Lecture on May 3, 2006 in Padova, Italy. I always admired Stan Korsmeyer, one of the greatest scientists and my good friend, as a man with full of humanity and dignity. As all our colleagues know, he conducted pioneering work on the regulation of apoptosis, identifying the key genetic mechanisms that govern cell death and survival and defining the role of cell death in cancers. His achievements will remain forever as the milestone of biological/medical science. I also would like to take this opportunity to re-express my hearty wishes to Mrs. Susan Korsmeyer and their beloved children for their success, good health, and happiness.

Introduction

Cytokines have gained much attention in biological sciences and medicine. Cytokines consist of several families of soluble molecules, such as interferons (IFNs), interleukins (ILs) and many others, that transmit signals to cell interior, eliciting variety of responses from a cell. It is now widely known that these cytokines play critical roles in many biological systems, such as oncogenesis and immunity. However, until the late 1970's, the structure and function of these cytokines remained elusive, as well as the underlying mechanisms of the signal transmission and regulation of their expression. Indeed, addressing these issues was hampered by the facts that these molecules are usually produced simultaneously at very low levels in many cell types, making it difficult to obtain in pure form, and that many cytokines may have multiple biological activities. Furthermore, despite of the prospects of cytokines for clinical application, it was difficult to obtain sufficient amount of each cytokines in pure form. My research career on cytokines began from the characterization of the human fibroblast IFN gene (now referred to as IFN-β) in 1979 (1). In collaboration with Dr. Charles Weissmann and colleagues, we elucidated the primary structure of two IFN proteins (IFN-α and -β; collectively called type I IFNs) and demonstrated that IFN-α and IFN-β genes constitute a gene family; this turned out to be the first of the numerous cytokine gene families to be identified later (2). We also identified and characterized a human interleukin gene, the IL-2 gene and generated recombinant IL-2, thereby enabling the study of the molecular basis of lymphocyte proliferation (3). The availability of these recombinant cytokines has made their clinical applications in the treatment of cancer, hepatitis and multiple sclerosis, and their use in studies of molecular signaling mechanisms possible. It also became possible to study the molecular mechanisms underlying the regulation of cytokine gene expression (Fig. 1).

Subsequently, we and others identified regulatory

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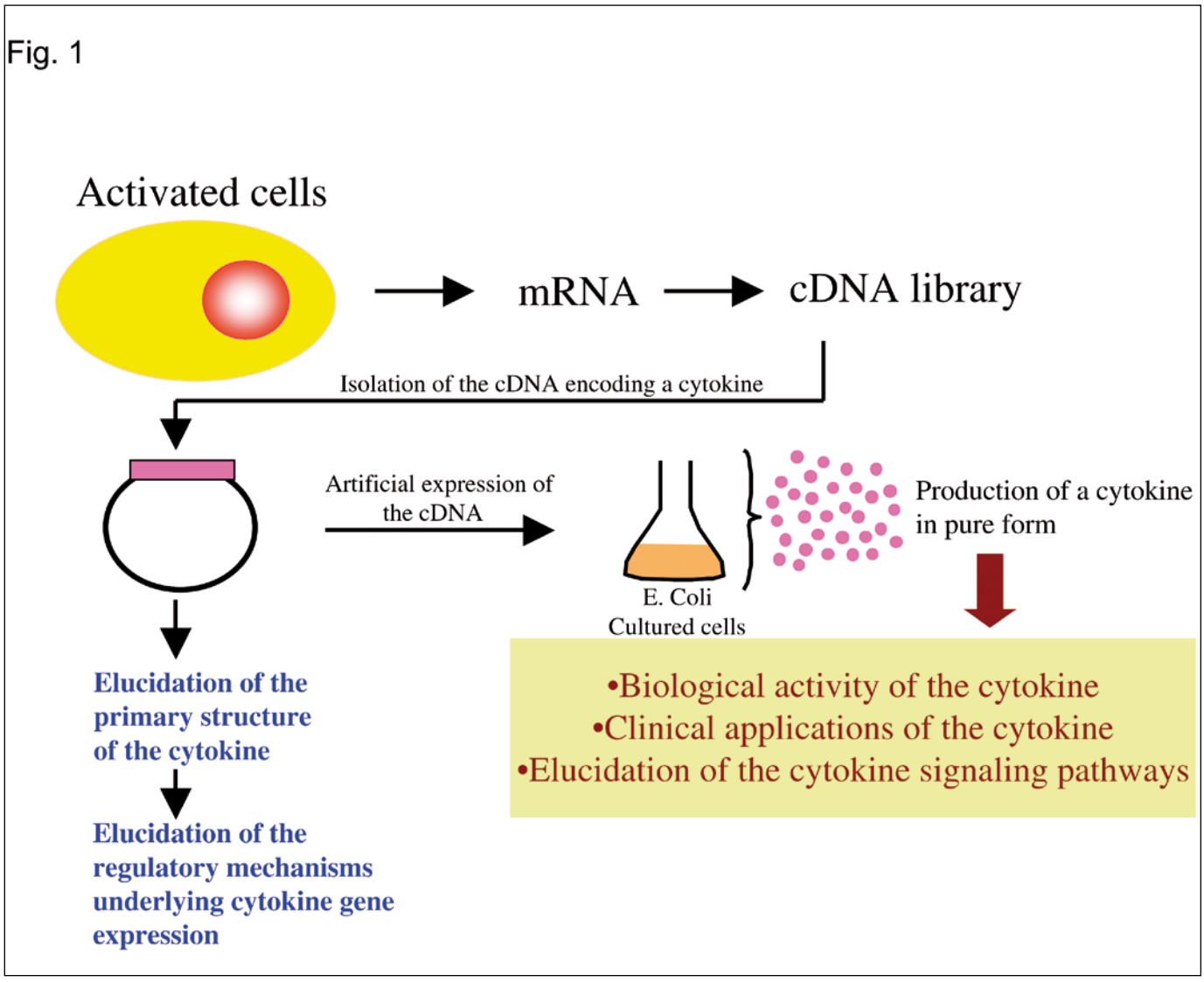

Fig. 1. Molecular characterization of the cytokine systems

Cytokines are usually produced simultaneously at very low levels in many cell types, therefore making it difficult to obtain in pure form. Furthermore, many cytokines may have multiple biological activities. The molecular analysis of cytokines began by isolating the cytokine genes. The availability of these recombinant cytokines has made their clinical applications in the treatment of cancer, hepatitis and multiple sclerosis, and their use in studies of molecular signaling mechanisms possible. The identification of cytokine genes was also the inception of cytokine gene regulation at the molecular level.

elements within the IFN-β gene promoter. Further research on cytokine gene expression and signaling led us to the discovery of a family of transcription factors, the interferon regulatory factors (IRFs; refs (4, 5)). The mammalian IRF family comprises nine members and they commonly contain a well-conserved N-terminal DNA-binding domain (DBD) of about 120 amino acids (Fig. 2). This sequence is now commonly termed ISRE (IFN-stimulated response element), and these elements are also found in the promoters of the IFN genes as well as in those of many other genes involved in immunity and oncogenesis (5). We demonstrated, in collaboration with other groups, the important and broad functions of IRF-1 and IRF-2 in the regulation of interferon responses and oncogenesis, as well as other immune functions, such as the $CD4^+$ T cell response and differentiation of natural killer and dendritic cells. We also elucidated the general regulatory mechanisms of IFN-α/β gene induction involving two other members of the IRF family, IRF-3 and IRF-7. More recently, we also found a new link between IFN signaling and p53.

The importance of the IRF family members has been further corroborated with the recent demonstration of their key roles in Toll-like receptor (TLR) signaling in innate and adaptive immune responses. The TLR family consists of as many as 13 germline-encoded transmembrane receptors in mammals, and each TLR recognizes various pathogen-associated molecular patterns (PAMPs) derived from bacteria, viruses, fungi and protozoa (6, 7). All TLRs contain intracellular Toll-interleukin-1 receptor (TIR) domains, which transmit downstream signals via the recruitment of TIR-containing adaptor proteins such as MyD88, the TIR-associated protein (TIRAP), the TIR domain-containing adaptor-inducing IFN (Trif) and the Toll-receptor-associated molecule (TRAM) (6, 7). The MyD88-dependent pathway, which is the best studied pathway, recruits several effector molecules such as IL-1 receptor-associated kinases 1/4 (IRAK1/4) and tumor necrosis factor receptor-associated factor 6 (TRAF6) (6, 7). These molecules are linked to at least three major downstream pathways; the NF-κB pathway, the pathway involving mitogen-activated protein kinases (MAPKs), and the IRF pathways.

We summarize below our recent findings, particularly focusing on the IFN signaling and p53, and the roles of IRFs in TLR signaling that is known to be critical for effective mounting of the anti-tumor immune responses.

I. Regulation of p53 responses by IFNs

Swift elimination of undesirable cells is an important feature in tumor suppression and immunity. The tumor suppressor p53 and IFN-α/β are essential for induction of apoptosis in cancerous cells and in antiviral immune responses, respectively, but little is known about their interrelationship. p53 is a pro-apoptotic protein required for the programmed death of tumour cells in response to DNA damage, and IFN-α/β are known to be critical for anti-viral immune responses. The successful use of IFN-α/β for the treatment of some types of human cancer has indicated that there might be a link between these anti-tumour and anti-viral responses — both of which require the rapid elimination of 'undesirable' host cells.

When mouse embryonic fibroblasts (MEFs) and the hepatic cancer cell line HepG2 were treated with IFN-α/β, the level of p53 protein was increased in a dose-dependent manner. IFN treatment did not affect the half-life of p53, and so does not increase protein degradation. IFN-β induced the expression of 53 mRNA by MEFs, indicating that gene transcription is increased. The mouse and human TP53 genes were both shown to contain IFN-stimulated response elements (ISREs) in their promoter or first intron, which are known to be activated by a transcription factor complex containing IFN regulatory factor 9 (IRF9); p53 induction in response to IFN-β was not observed in MEFs deficient in the IRF9 gene (8).

IFN-β stimulation did not induce the serine phosphorylation and hence activation of p53 protein and had no effect on the induction of p53 target genes. Therefore,

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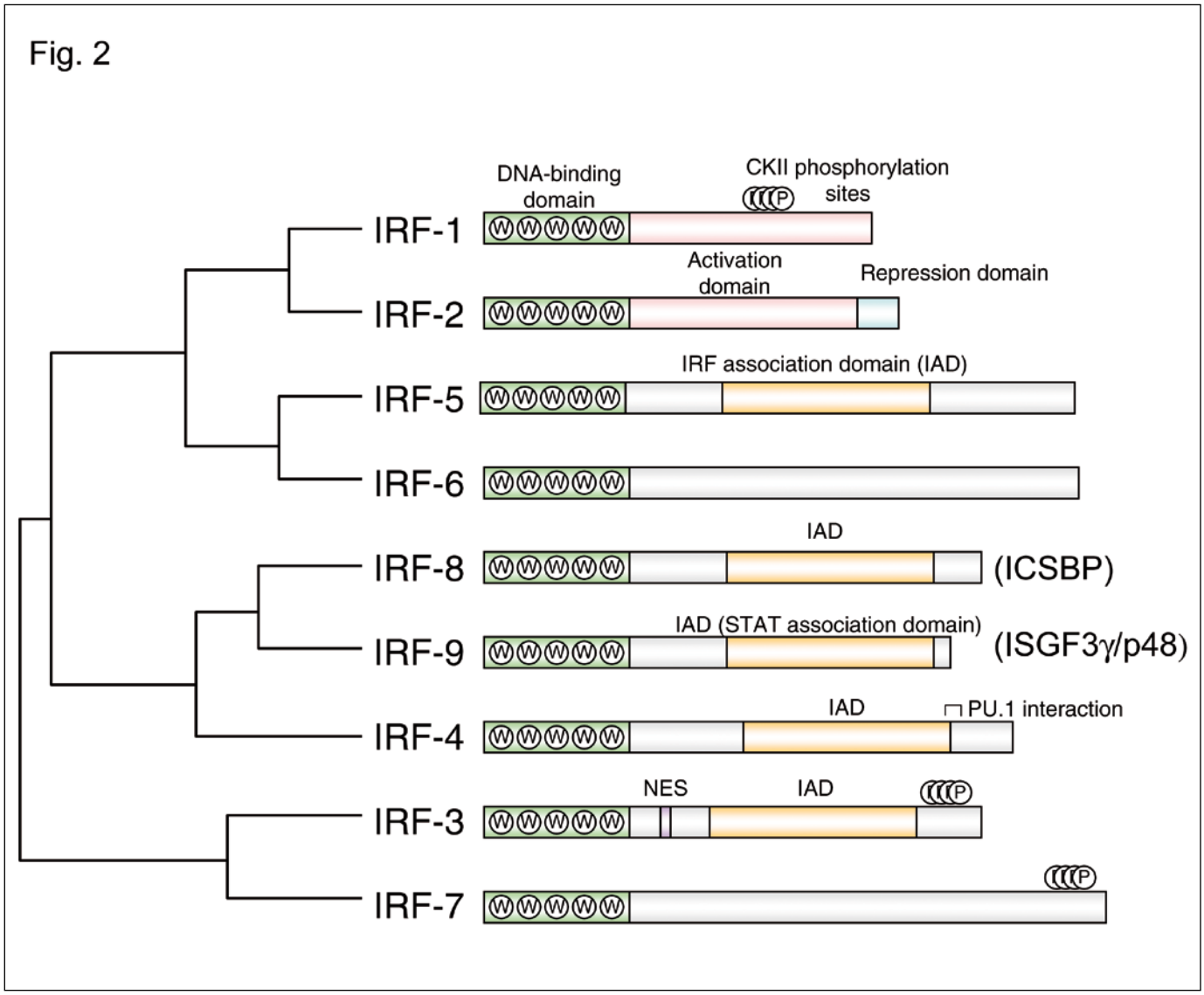

Fig. 2. The IRF family transcription factors

The mammalian IRF family was originally discovered in the context of IFN gene induction, and it comprises nine members; IRF-1, IRF-2, IRF-3, IRF4/Pip/ICSAT, IRF-5, IRF-6, IRF-7, IRF-8/ICSBP (interferon consensus sequence binding protein), and IRF-9/ISGF3γ (interferon-stimulated gene factor 3γ) (ref. 5). The family members commonly contain a well-conserved N-terminal DNA-binding domain (DBD) of about 120 amino acids and recognizes the consensus DNA sequence, 5'-GAAANNGAAA$^{G}/_{C}{}^{T}/_{C}$-3'. This sequence is now commonly termed ISRE (IFN-stimulated response element), since it was identified in the promoters of genes induced by type I IFNs.

although type I IFNs do not activate p53, by increasing the level of p53 protein, they increase the sensitivity of cells to stress stimuli that activate p53. Indeed, we have shown that the interaction between IFN and p53 pathways has implications for defence against both tumours and viruses. The human papilloma virus (HPV) protein E6 induces the degradation of p53 and, together with another oncoprotein such as **H-ras**, *can induce the transformation of primary MEFs. However, when IFN-β was added, the level of p53 protein was restored and there was a marked decrease in the number of transformed colonies (8).*

In terms of anti-viral responses, MEFs infected with various viruses were shown to have marked phosphorylation of p53. The apoptosis of virus-infected cells mediated by p53 was inhibited in MEFs deficient for IFN-α/β receptor 1 (IFNAR1), whereas p53 phosphorylation was not inhibited, which supports the idea that IFN signaling is required for p53 sensitization rather than activation. p53-deficient MEFs infected with vesicular stomatitis virus gave a higher virus yield than wild-type MEFs, which indicates that p53-dependent apoptosis (enhanced by IFN-α/β signalling) is important for controlling virus replication (Fig. 3; ref. (8)).

Our strudy could have important implications for cancer therapy as it indicates that IFN-treated cells should be more susceptible to DNA-damaging chemotherapeutic agents such as 5-fluorouracil (5-FU), allowing lower doses to be used. In this regard, it is interesting to note that the combination of IFN and 5-FU has been applibed, with ntable sucess, to the treatment of hepatic cancers (9) : It remains to be clarified whether the IFN's function in the treamnet is to indice p53 protein. In summary, our study revealed a hitherto unrecognized cooperation of p53 and IFN-α/β in tumor suppression and antiviral immunity, and may have therapeutic implications.

II. TLR4 signaling and activation of IRF-3

TLR4 is activated by LPS or the lipid A component of Gram-negative bacteria, as well as by some viral components such as the F (fusion) protein of the respiratory syncytial virus or the envelope proteins of the mouse mammary tumor virus and Moloney murine leukemia virus (10-12). TLR4 signaling results in the induction of the IFN-β gene but not the IFN-α gene (13). It is not clear whether TLR4 is involved in antiviral responses, but TLR4-mediated IFN-β induction is critical for the maturation of dendritic cells (DCs) and induction of acquired immunity (14).

TLR4 signaling utilizes two signaling pathways, namely, the MyD88-TIRAP and TRAM-Trif pathways (7). IFN-β gene induction via TLR4 is mostly dependent on the TRAM-Trif pathway, whereas the induction of proinflammatory cytokine genes, such as tumor necrosis factor (TNF)-α and Interleukin (IL)-6 genes, is dependent on both MyD88 and TRAM-Trif (7). The TRAM-Trif pathway is linked to TANK-binding kinase 1 (TBK1) for IFN-β gene induction, as the induction was abolished in cells deficent in the Tbk1 gene (15, 16). IRF-3 is essential for this IFN-β induction pathway that also induces other genes of the immune system, for example, some chemokine genes (13, 17) (Fig. 1). IRF-3 was activated within 30 min of stimulation and the induction of IFN-β in response to LPS was abolished in $Irf3^{-/-}$ DCs (13, 18). Consistently, $Irf3^{-/-}$ mice exhibited resistance to LPS-induced endotoxin shock (13), for which IFN-β induction is critical (19). Thus, IFN-β induction by TLR4 is mediated by an IRF-3 homodimer via its phosphorylation by TBK1. TNF-α induction by LPS also appears to be IRF-3-dependent, but IRF-3 may participate indirectly in TNF-α gene induction (18).

III. TLR3 signaling and IRFs

TLR3 recognizes dsRNA and was reported to be involved in defense against the mouse cytomegalovirus and West Nile virus (20, 21). TLR3 is also involved in the recognition of Leishmania donovani promastigotes (22), suggesting that structures other than dsRNA are also recognized by TLR3. Similar to TLR4, the activation of TLR3 can induce type I IFN expression via a MyD88-independent, Trif- and TBK1-dependent signaling pathway. Indeed, the induction of IFN-α/β

Fig. 3

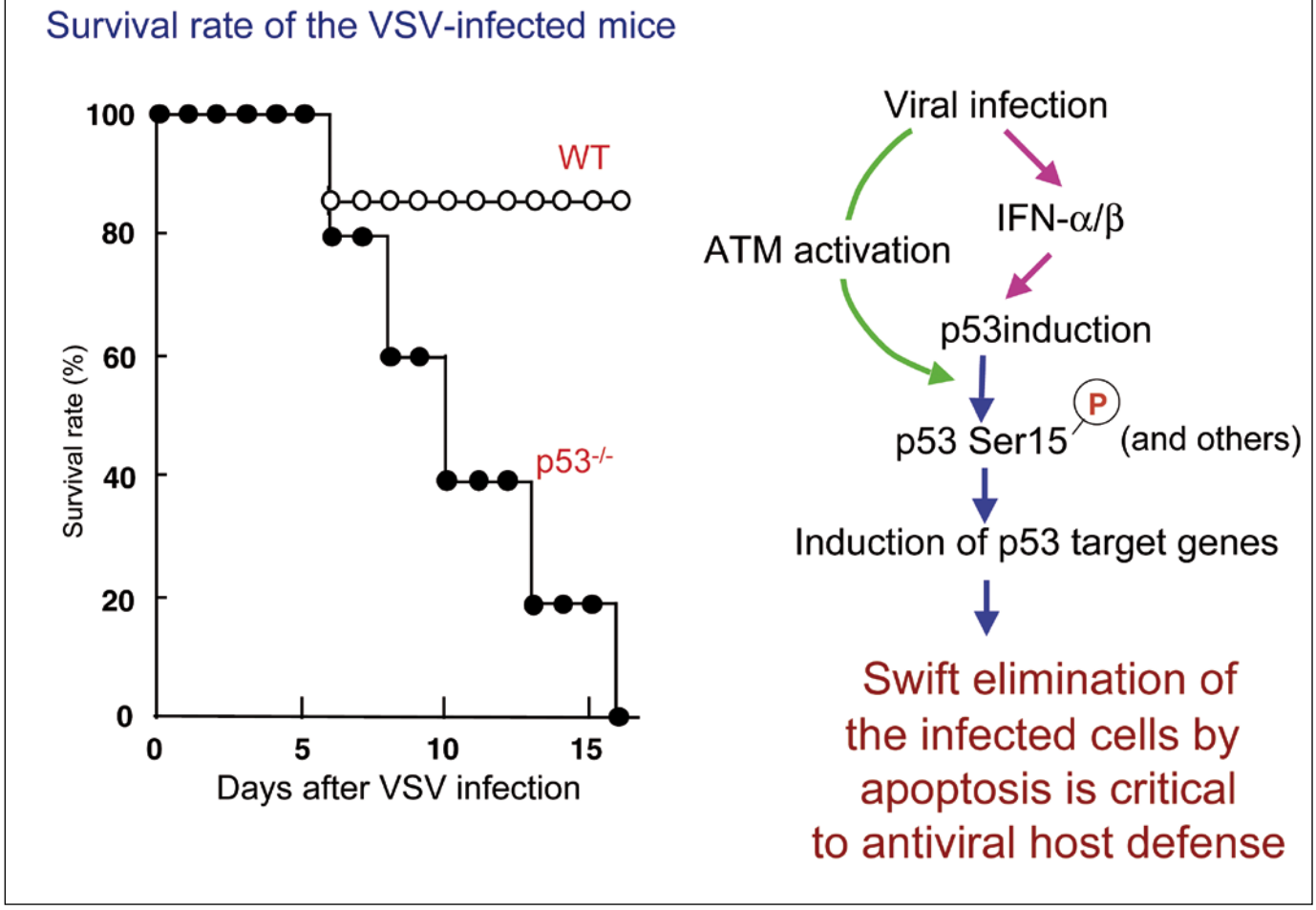

Fig. 3. Function of the p53 tumor suppressor in antiviral host defense

Cells infected with various viruses have marked phosphorylation of p53. The apoptosis of virus-infected cells mediated by p53 was inhibited in cells deficient for IFN signaling, whereas p53 phosphorylation was not inhibited. Therefore, IFN signaling is required for p53 sensitization rather than activation (Right panel). Consistent with the in vivo data showing the critical role of p53 in the swift elimination of virally infected cells by apoptosis, p53-deficient mice are highly vulnerable to infection by vesicular stomatitis virus (Left panel). See text and ref. (8) for details.

genes by synthetic dsRNA, poly(I:C) was severely impaired in Trif$^{-/-}$ or Tbk1$^{-/-}$ cells (15, 16, 23). Although IRF-3 plays an essential role in this induction, the poly(I:C)-mediated induction of IFN-α/β mRNAs was still observed in Irf3$^{-/-}$ DCs and this residual induction was completely abolished in DCs from Irf3 and Irf7 doubly deficient mice (K.H., unpublished observation). Therefore, IRF-7 is also required for Trif-mediated signaling for the full induction of the IFN-α/β genes. It was reported that PI3K activity might be additionally required for the full activation of IRF-3 in TLR3 signaling.

There are certain caveats associated with the interpretation of the results of experiments using poly(I:C) as a TLR3 ligand, because poly(I:C) can be recognized by other molecules of the cytosolic sensing system; therefore, careful studies will be required to dissociate the TLR3 signaling pathway from the TLR-independent, cytosolic pathway.

IV. Essential role of IRF-7 for robust IFN induction by TLR9 subfamily

Much attention has been focused on the high-level induction of IFN-α/β in plasmacytoid DCs (pDCs), a small subset of DCs (24). pDCs use the TLR system (in particular, the TLR9 subfamily members, TLR7 and TLR9) for this robust IFN induction; the induction of IFN expression is abolished when pDCs are deficient in these TLRs. DNA viruses such as herpes simplex virus (HSV) contain a large number of unmethylated CpG motifs in their genome, which are recognized by TLR9 and induce robust IFN production in pDCs (25, 26). Similarly, TLR7/8 signaling is essential for IFN induction against influenza virus or vesicular stomatitis virus (VSV) infection by recognizing viral genomic single-stranded RNA (ssRNA)(27-29). In contrast to TLR3- or TLR4-mediated Trif-dependent IFN induction, the TLR9 subfamily members exclusively utilize MyD88 as the signaling adaptor (7).

The MyD88 adaptor selectively interacts with IRF-7 (not with IRF-3) in the cytoplasm (30-32) (Fig. 1). Fluorescence microscopy studies showed that IRF-7 colocalized with MyD88 in endosomal vesicles, whereas IRF-3 did not. Moreover, fluorescence resonance energy transfer (FRET) analysis revealed a direct interaction between IRF-7 and MyD88. When cells expressing fluorescently tagged IRF-7 were stimulated with an IFN-inducing TLR9 ligand, that is, A- or D-type unmethylated CpG DNA (CpG-A; ref. (33)), the nuclear translocation of IRF-7 was evoked. Upon the cotransfection of expression plasmids for MyD88 and IRF-7 together with the IFN-β promoter-driven reporter gene, the reporter gene was strongly induced, and similar observations were obtained by coexpressing TRAF6 and IRF-7. These observations suggest that IRF-7 interacts with and is activated by MyD88 and TRAF6 upon TLR9 stimulation to induce IFN genes.

Definitive evidence has been obtained, using Irf7$^{-/-}$ mice, for the selective requirement of IRF-7 in IFN-α/β gene induction in pDCs via TLR9 subfamily activation (34) (Fig. 4). Spleen-derived pDCs from Irf7$^{-/-}$ mice exhibited a profound defect in IFN-α/β induction either by viral infections or synthetic TLR ligands (CpG-A and ssRNA). It was also shown that the MyD88-IRF-7 pathway was critical for the induction of CD8^{+} T cell responses in vivo (34).

The mutation studies of MyD88 revealed that the death domain of MyD88 is responsible for MyD88 interaction with IRF-7 (ref. (30)). The death domain also interacts with the IRAK family of serine/threonin kinases, the signal transducers between MyD88 and TRAF6. The involvement of IRAKs in the IRF-7 pathway is supported by the observation that pDCs derived from Irak4$^{-/-}$ or Irak1$^{-/-}$ mice had a defect in IFN-α production induced following the activation of the TLR9 subfamily members (30, 35). Consistently, IRAK1, which is activated by IRAK4, phosphorylated IRF-7 in vitro (35) (Fig. 1). As IRAK4 is also essential for NF-κB activation, it presumably acts upstream of IRAK1 in the signaling and participates in the IRF-7 pathway via the phosphorylation of IRAK1(35).

V. Regulation of MyD88-IRF-7 signaling pathway by vesicular trafficking

An unanswered question was why pDCs but not other cell types, such as cDCs, produce large amounts of IFNs in response to the same TLR9 ligand. It was assumed that a higher level of constitutive expression of IRF-7 in pDCs than that in cDCs may be responsible, but this does not fully account for the robust IFN induction (32, 36). Instead, a mechanism that likely accounts for the specific ability of pDCs to produce IFN-α/β is the spatiotemporal regulation of TLR7 and TLR9 signalings (32).

In pDCs, the IFN-inducing TLR9 ligand CpG-A localized for a long period in the endosomal compartment, where the MyD88-IRF-7 complex preferentially localizes (32). In contrast, the same ligand localized in lysosomes in cDCs. Thus, pDCs seem to use a unique mechanism by which they retain TLR9-bound CpG-A in endosomes, and a prolonged signaling may allow the phosphorylation of de novo synthesized IRF-7 and the activation of the positive feedback system to induce a robust IFN-α/β production. In this regard, it is interesting that viruses such as VSV and HSV also reside in an endosomal compartment after infection (37, 38) and there is evidence supporting the importance of this localization for IFN induction (26). Although the mechanisms that determine endosomal trafficking in CpG-stimulated pDCs still remain unknown, one may speculate that one or more molecules are selectively expressed in pDCs and assist the endosomal longevity of TLR9 signaling. It is worth noting that CpG-B, which undergoes rapid lysosomal trafficking, more strongly induces proinflammatory cytokines than CpG-A; it is possible that lysosomal TLR9 signaling may be crucial for effectively evoking this response (39).

VI. TLR signaling and IRF-5

Interestingly, it has been shown that IRF-5 also interacts with MyD88 and TRAF6 (ref. (8)) (Fig. 1). Unlike IRF-7, which binds to the death domain of MyD88, IRF-5 interacts with the middle region (the intermediary domain and part of the TIR domain) of MyD88 (ref. (40)). After TLR9 activation, IRF-5 was found to translocate to the nucleus and bind to the promoter region of the IL-12p40 gene, which contains ISRE (8). The critical function of IRF-5 in TLR signaling is underscored by the observation that the induction of proinflammatory cytokines, such as TNFα, IL-6 and IL-12 p40, by the ligands of TLR3, TLR4, TLR5, TLR7 and TLR9 was severely impaired in macrophages and cDCs from Irf5$^{-/-}$ mice (8). Furthermore, Irf5$^{-/-}$ mice showed an increased resistance to lethal shock induced by CpG-B or LPS (8). These observations collectively indicate that TLR stimulation commonly induces the formation of the MyD88-IRF-5-TRAF6 complex and results in the nuclear translocation of IRF-5 to induce proinflammatory cytokines (Fig. 4). Although the upstream mediators of the IRF-5 pathway await identification, it is likely that IRF-5 is phosphorylated in the MyD88 complex and transmigrates to the nucleus. A recent report showed that although TBK1 could induce IRF-5 phosphorylation, the TBK1-induced phosphorylation of IRF-5 did not stimulate IRF-5 nuclear translocation (41).

It is not fully understood how TLR signaling diverges from MyD88 to the IRF-5 and NF-κB pathways. It is possible that the ligand receptor-interaction-mediated formation of multimolecular complexes anchored by MyD88 may permit the selective positioning of specific molecules into discrete subcellular compartments, and the physical inclusion or exclusion of signaling molecules from particular sites within a cell may govern the magnitude, duration and type of downstream signaling pathways engaged, as exemplified in the above-described MyD88-IRF-7 pathway. More recently, we found another interesting facet of IRF5 in anti-tumor immunity. In the IRF5-defient mice, massive lung metastasis of the B16 melanoma cells was observed (A. Takaoka, T.T., unpublished data). It is therefore interesting to examine whether the suppression of tumor metastasis mediated by IRF5 is mediated by TLR signaling.

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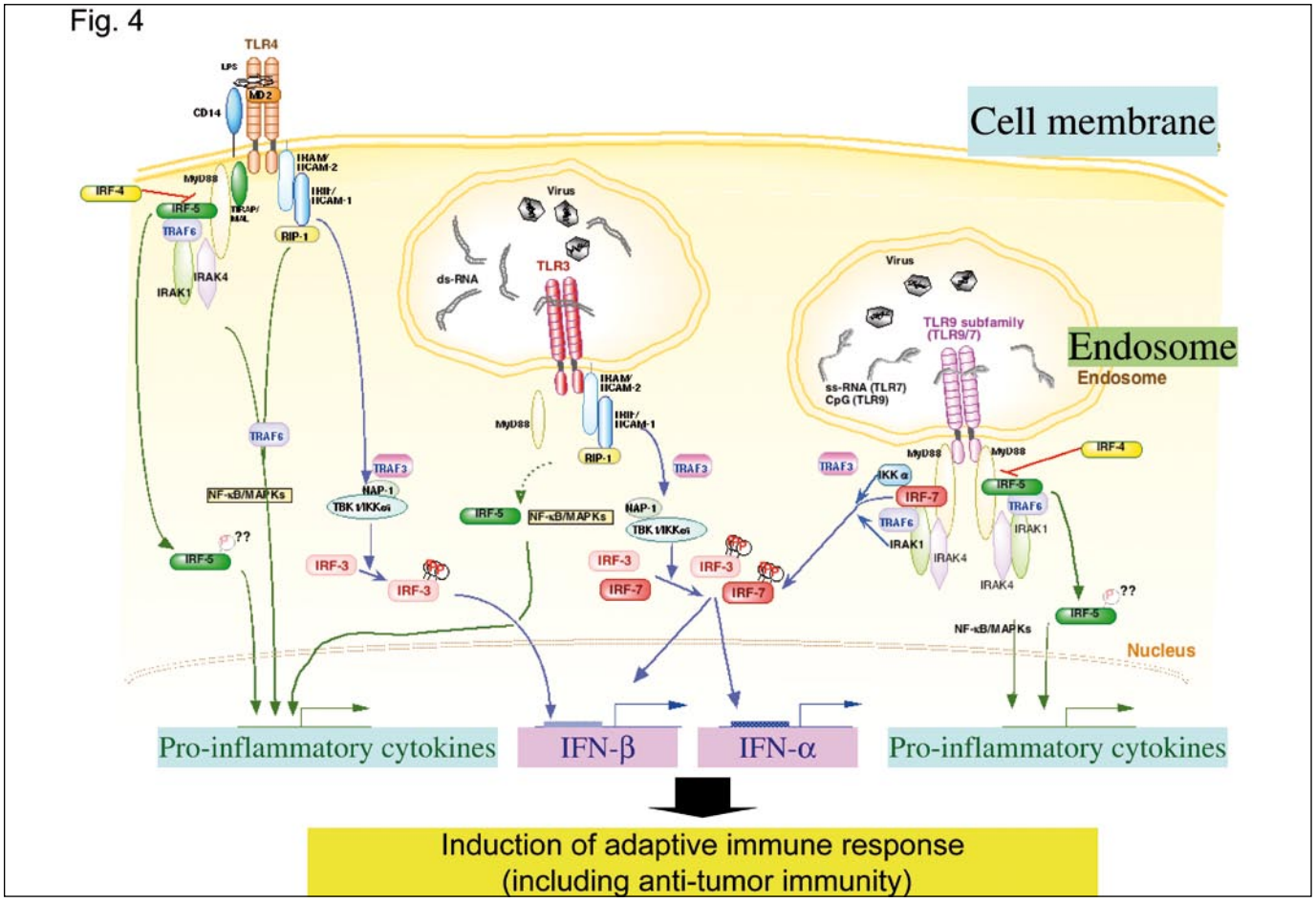

Fig. 4. Activation of IRFs by TLR signaling pathway
TLR signalling is thought to be critical for the activation of innate immunity and subsequent induction of adaptive immunity including anti-tumor immunity. Several IRF-family members are involved in the MyD88-dependent and/or -independent signalling pathways, contributing to the gene-expression programme induced by TLRs. TLR4 signals through at least four adaptors: TIRAP, MyD88, TRAM and TRIF. TRAM and TRIF mediate the IRF3 activation. TRIF is linked to TBK1 activation through NAP1 and TRAF3. TBK1 hosphorylates IRF3 and activated IRF3 induces IFN-β and other target genes (Left). In TLR3 signaling, the TRIF pathway is activated and, in this case, IRF3 and IRF7 are both actiivated, however, it remains to be clarified to what extent this pathway cobntribute to IFN gene induction (Middle). In TLR7/9 signaling, IRF7 directly binds to MyD88 on endosomes and regulates the type I IFN gene induction programme. Upon TLR7 or TLR9 stimulation, IRF7 interacting with MyD88 is activated by IRAK4/IRAK1/IKKα pathway (Right). IRF5 interacts with and is activated by MyD88 and TRAF6 by an as yet unknown mechanism. Activated IRF5 translocates to the nucleus to activate proinflammatory cytokine gene transcription, presumably in cooperation with NF-κB. It remains to be clarified if IRF5 needs to interact with DNA (as depicted here) for its function. IRF4, which is transcriptionally induced by TLR stimulation, binds to MyD88 in a region overlapping with that of IRF5, thereby inhibiting the further binding of IRF5 to MyD88 and attenuating the MyD88-dependent activation of IRF5. See text for further details.

VII. Negative regulation of TLR signaling by IRF-4

Further studies on other IRF family members revealed that IRF-4 also interacts with MyD88 via the middle region of MyD88, which is the same region for IRF-5 binding (40), and suggested that IRF-4 might compete with IRF-5 but not with IRF-7 for MyD88 interaction. Indeed, the induction of proinflammatory cytokines by TLRs, which is dependent on IRF-5, was markedly enhanced in peritoneal macrophages derived from Irf4$^{-/-}$ mice. On the other hand, the IRF-7-dependent induction of IFN-α in pDCs from Irf4$^{-/-}$ mice remained the same as that in wild-type pDCs. Furthermore, Irf4$^{-/-}$ mice were highly sensitive to CpG-induced shock. As IRF-4 mRNA is induced upon TLR activation (40), IRF-4 appears to participate in the negative feedback regulation of TLR signaling. Induced IRF-4 binds to MyD88 at a region overlapping with the binding region of IRF-5, thereby inhibiting the further binding of IRF-5 to MyD88 and attenuating the MyD88-dependent activation of IRF-5 (Fig. 4).

VIII. Future prospects

It is remarkable that study on the IFN-α/β system, carried out by many scientists, significantly contributed to our understanding of the mechanisms of cytokine action, oncogenesis and immune response. In fact, the critical role of Janus family protein tyrosine kinases (JAK kinases), Signal Transducers and Activators of Transcription (STATs), and IRFs have all been identified in the context of the IFN induction and action, and their broad functions in other biological systems are widely appreciated by now. It is remarkable that many IRFs participate in the MyD88-dependent signaling pathway, carrying their distinct mission with each other, and we will perhaps identify more IRFs functioning in TLR signaling in future studies. Some IRFs need not bind to the promoter region of its target genes, as demonstrated by the interaction of IRF-3 with NF-κB (17, 42, 43), and it will not be surprising to see more examples in the future, particularly in conjunction with NF-κB. It is therefore interesting to study further how MyD88, apparently interacting with so many signaling molecules and transcription factors, manages to diverge its functions to adequately regulate the gene regulation network.

It is also probable that additional interactions of IRFs with signaling molecules, will be identified in future studies, and these efforts should lead to a more complete understanding of mechanisms underlying IRF regulation and function. These future studies may also offer a new molecular basis for cancer and immune therapies.

Acknowledgements

I thank Dr. A. Takaoka for valuable discussion and help. This work was supported by KAKENHI (Grant-in-Aid for Scientific Research) on Priority Areas "Integrative Research Toward the Conquest of Cancer" from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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19th Pezcoller Symposium, Trento, Italy June 14-16, 2007

Hypothesis driven clinical investigation in cancer

Co-Chairmen
William G. Kaelin, Enrico Mihich and Charles L. Sawyers

Program Committee
Jose Baselga, Marco Pierotti and David P. Carbone

Cancer chemotherapy is being greatly enriched by the development of treatments which affect molecular targets uniquely present in cancer cells and essential for tumor growth and progression. This Symposium is focused on clinical investigations aimed at validating targets identified in basic preclinical studies and at exploiting them through the development of rationally designed and hypothesis driven clinical trials. A session will be devoted to the proof of concept which derives from recent successes in the application of these ideas. As molecular targets are not equally present in all patients with the same tumor type, it is important to identify their presence and function in a given patient in order to predict his/her response to a given molecular target oriented agent: this topic will be extensively discussed. A session will be devoted to the identification of markers of drug effectiveness which could lead to the optimization of a given regimen. The two final sessions will be focused, respectively, on novel preclinical and clinical investigations and on opportunities for the development of new specific molecular target oriented therapies. The program of the Symposium provides equal time to presentations and to discussions and thus gives to the participants numerous opportunities for interactions with leaders in the fields discussed and for cross fertilization among investigations of diversified expertise. Submission of posters on work done in the areas discussed are encouraged and the three best posters will be given the opportunity to be presented orally. For scientific issues concerned with the program of the Symposium contact Dr. Enrico Mihich, Roswell Park Cancer Institute, Buffalo, NY, USA, fax +716-845-3351, email: enrico.mihich@roswellpark.org.
For practical matters concerned with registration and local arrangements, contact Giorgio Pederzolli, Pezcoller Foundation, Trento, Italy, Fax +39-0461-980350, email: pezcoller@pezcoller.it.

More information about the simposium on our web site: www.pezcoller.it

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2007 Pezcoller Foundation-FECS Recognition for Contribution to Oncology

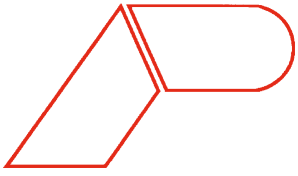
The Federation of European Cancer Societies and the Pezcoller Foundation are pleased to announce the "2007 Pezcoller Foundation-FECS Recognition for Contribution to Oncology".

The Pezcoller Foundation was established in 1982 through a most generous donation from Professor Alessio Pezcoller, a dedicated Italian surgeon, who devoted his life to his profession. Professor Pezcoller not only made important contributions to medicine, but through his generosity and foresight has provided his lifetime's savings for others to do likewise.
In the past, until 1997, the Pezcoller Foundation gave an award in collaboration with the European School of Oncology. The Pezcoller Foundation-FECS Recognition for Contribution to Oncology builds up upon this tradition.
In 2007 in collaboration with the Federation of European Cancer Societies, the Pezcoller Foundation-FECS Recognition for Contribution to Oncology will be awarded to a single individual for his/her professional life dedication to the_improvement of cancer treatment, care and research.
Nominations for the 2007 Pezcoller Foundation-FECS Recognition for Contribution to Oncology will be accepted for candidates regardless of race, sex or nationality. Institutions, groups or associations are not eligible. Self nominations will not be considered. Candidates must be nominated on the official form by one who is, or has been, affiliated with a university or medical institution.
A curriculum vitae and description of the professional contribution to Oncology of the candidate should be included with the application form.

Nominators are requested to keep their nomination confidential and to refrain from informing the nominee.
The awardee will be selected by an International Committee appointed by the FECS President with the agreement of the Council of the Pezcoller Foundation. The decision by the Pezcoller Foundation concerning the 2005 winner will be taken in March 2007.
The award consists of a prize of € 30.000 and a commemorative plaque.
The award ceremonies will be held in Rovereto (Italy) and in Barcellona, during ECCO 14 - The European Cancer Conference with a plenary lecture being delivered on Monday 24th September 2007.

Questions about the nomination process should be directed to the FECS – Federation of European Cancer Societies – Avenue E. Mounier, 83 – B-1200 Brussels – Tel. 32 2 7752931 – Fax 2 7750200 – e-mail: carine@fecs.be

Completed nomination form must be received by 31 December 2006 in order to be considered.
Nomination forms and supporting documents should be sent to:
2007 Pezcoller Foundation FECS Recognition for Contribution to Oncology.
Federation of European Cancer Societies
Avenue E. Mounier, 83 – B-1200 Brussels.



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