

CNIO Cancer Conference

Inflammation and Cancer

Madrid, May 22-24, 2006

Organisers:

Raymond DuBois. The Vanderbilt-Ingram Cancer Center, Nashville, USA

Curtis Harris. National Cancer Institute, NIH, Bethesda, USA

Jorge Moscat. Molecular Biology Centre "Severo Ochoa", CSIC-UAM,
Madrid, Spain

Manuel Serrano. Spanish National Cancer Research Centre (CNIO),
Madrid, Spain

■ CNIO Auditorium

Centro Nacional de Investigaciones Oncológicas
Melchor Fernández Almagro, 3
E-28029 Madrid, Spain
www.cnio.es





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CNIO Cancer Conference: Inflammation and Cancer

Auditorium of the Spanish National Cancer Research Centre, CNIO
(Melchor Fernández Almagro, 3, E-28029 Madrid) May 22-24, 2006

Monday, May 22	Tuesday, May 23	Wednesday, May 24
Welcome address / 09:30h-09:40h Mariano Barbacid. CNIO Director	II. Crosstalks in Inflammation and carcinogenesis / 09:30h-19:10h Chair: Tim Billiar	III. Cellular stress responses in inflammation and cancer / 09:30h-12:20h Chair: Curtis Harris
I. The NF-κB pathway / 09:40h-19:20h Chair: Raymond N. DuBois	Timothy R. Billiar. Pittsburgh (USA) Santos Mañes. Madrid (Spain)	Manuel Serrano. Madrid (Spain) Peter Hasselblat. Vienna (Austria)
Raymond N. DuBois. Nashville (USA) Seth Rakoff-Nahoum. New Haven (USA) Yinon Ben-Neriah. Jerusalem (Israel)	Lisa Coussens. San Francisco (USA)	Masayuki Yamamoto. Tsukuba (Japan)
<i>Coffee break and Poster session (11:20 - 12:20)</i>	<i>Coffee break and Poster session (11:30 - 12:30)</i>	<i>Coffee break (10:30 - 11:00)</i>
Jorge Moscat. Madrid (Spain) Mirna Perez-Moreno. New York (USA) Neil D. Perkins. Dundee (UK)	Alicia G. Arroyo. Madrid (Spain) Michael Thun. Atlanta (USA)	Curtis Harris. Bethesda (USA)
<i>Lunch (14:00 - 15:30)</i> Chair: Michael Karin	<i>Lunch (14:10 - 15:30)</i> Chair: Martin J. Blaser	Poster prize announcement and Closure (12:20h) <i>Lunch (12:30)</i>
Michael Karin. La Jolla (USA) Angel Nebreda. Madrid (Spain) Sankar Ghosh. New Haven (USA)	Martin J. Blaser. New York (USA) Maria C. Guerra. Madrid (Spain) Zena Werb. San Francisco (USA)	
<i>Coffee break and Group Picture (17:10 - 17:40)</i>	<i>Coffee break (17:10 - 17:30)</i>	
Veronique Baud. Paris (France) Ann Richmond. Nashville (USA)	Albena Dinkova-Kostova. Baltimore (USA) Manuel Fresno. Madrid (Spain) Xin-Wei Wang. Bethesda (USA)	

■ 2006 CNIO Cancer Conference: Inflammation and Cancer

Detailed Programme

Monday, May 22, 2006

09:30h Welcome address, **Mariano Barbacid**, CNIO Director

Session I: The NF- κ B pathway

Chair: **Raymond N. DuBois**

09:40 **Raymond N. DuBois**, Vanderbilt-Ingram Cancer Center, Nashville, USA
Inflammation and Cancer: Crosstalk between prostaglandin and cancer signaling pathways

10:20 **Seth Rakoff-Nahoum**, Yale University School of Medicine, New Haven, CT, USA
(Short talk) TLR-MyD88 dependent tissue repair response promotes intestinal tumorigenesis

10:40 **Yinon Ben-Neriah**, Hebrew University-Hadassah Medical School, Jerusalem, Israel
Molecular cues for the development and progression of inflammation-associated liver cancer

11:20h *Coffee Break and Poster Session I – Odd poster numbers*

12:20 **Jorge Moscat**, CBMSO, CSIC-UAM, Madrid, Spain
Bifunctional role of PKC ζ in inflammation and cell damage

13:00 **Mirna Perez-Moreno**, Rockefeller University, New York, USA
(Short talk) A Novel Role for p120^{ctn} in mediating inflammatory responses in skin

13:20 **Neil D. Perkins**, School of Life Sciences, University of Dundee, UK
Differential regulation of NF- κ B subunit function

14:00h *Lunch*

Chair: **Michael Karin**

15:30 **Michael Karin, University of California at San Diego, La Jolla, USA**
The IKK Complex: Providing a Link between Inflammation and Cancer

16:10 **Angel Nebreda, CNIO, Madrid, Spain**
(Short talk) Role of p38alpha MAP kinase as an oxidative stress sensor in oncogene-induced malignant transformation

16:30 **Sankar Ghosh, Yale University, New Haven, USA**
NF-kB: a mediator of inflammatory responses and cancer

17:10h Coffee Break and Group Picture

17:40 **Veronique Baud, Institut Cochin, Paris, France**
(Short talk) RelA repression of RelB activity induces selective gene activation downstream of TNFR

18:40 **Ann Richmond, Vanderbilt University, Nashville, USA**
NF-kB as a Potential Therapeutic Target for Malignant Melanoma

■ 2006 CNIO Cancer Conference: Inflammation and Cancer

Tuesday - May 23, 2006

Session II: Crosstalks in Inflammation and carcinogenesis

Chair: **Timothy R. Billiar**

- 09:30 **Timothy R. Billiar, University of Pittsburgh, Pittsburgh, USA**
Unique Features of the Death Induced Signaling Complex in Hepatocytes Exposed to TNF
- 10:10 **Santos Mañes, National Centre of Biotechnology, CSIC, Madrid**
Chemokines and Cancer Progression
- 10:50 **Lisa Coussens, University of California at San Francisco**
Inflammation, Proteolysis and Cancer

11:30h *Coffee Break and Poster session II – Even poster numbers*

- 12:30 **Hans Schreiber, University of Chicago, USA**
Role of CD11b Positive Immature Myeloid Cells in Tumor Promotion and Eradication
- 13:10 **Alicia G. Arroyo, CNIC, Madrid, Spain**
(Short talk) MTI-MMP and inflammation: MTI-MMP is involved in chemokine- and nitric oxide - induced angiogenesis and in monocyte migration
- 13:30 **Michael Thun, American Cancer Society, Atlanta, USA**
Risk benefit considerations regarding NSAIDs as anticancer agents

14:10h *Lunch*

Chair: **Martin J. Blaser**

15:30 **Martin J. Blaser, NYU Medical Center, New York**
How to influence people: The changing repertoires of *Helicobacter pylori*

16:10 **Maria C. Guerra, CNIO, Madrid, Spain**
(Short talk) Chronic pancreatitis and K-ras oncogenes are required to induce pancreatic ductal adenocarcinoma in adult mice

16:30 **Zena Werb, University of California at San Francisco, USA**
The dynamics of the inflammatory response to cancer

17:10h Coffee Break

17:30 **Albena Dinkova-Kostova, Johns Hopkins University, Baltimore**
Protection against oxidant and inflammatory stress: the role of inducers of the Phase 2 response

18:10 **Manuel Fresno, CBMSO, Madrid, Spain**
(Short talk) Bombesin induces cyclooxygenase-2 expression and migration in the human colon adenocarcinoma

18:30 **Xin-Wei Wang, National Cancer Institute, NIH, Bethesda**
Potential role of liver microenvironment in metastasis and recurrence of hepatocellular carcinoma

■ 2006 CNIO Cancer Conference: Inflammation and Cancer

Wednesday - May 24, 2006

Session III: Cellular stress responses in inflammation and cancer

Chair: **Curtis Harris**

09:30 **Manuel Serrano**, Spanish National Cancer Research Centre (CNIO), Madrid

Tumor suppression, senescence and aging

10:10 **Peter Hasselblat**, Research Institute of Molecular Pathology (IMP), Vienna, Austria

(Short talk) Functions of the transcription factor AP-1 (Fos/Jun) in colitis-associated cancer

10:30h Coffee Break

11:00 **Masayuki Yamamoto**, University of Tsukuba, Japan

Regulation by Nrf2-Keap1 System of Cellular Defense Mechanisms against Electrophiles and Carcinogenesis

11:40 **Curtis Harris**, National Cancer Institute, NIH, Bethesda

Microenvironment and Cancer: Inflammation and MicroRNA

12:20h **Poster prize announcement and Closure**

*Nature Reviews Cancer sponsors the poster prize at each CCC.
(This prize consists of a personal one-year subscription to the journal)*

12:30h Lunch

List of Posters (in alphabetical order of presenting author)

- 1 Dimitrios Balomenos** - CNB, Dept of Immunology and Oncology, Madrid, Spain
p21(WAF1/CIP1) regulates the NF-kB-dependent macrophage activation pathway and suppresses septic shock induction
- 2 Gaëlle Cane** - Institut de Signalisation, Biologie du développement et Cancer, Nice, France
C1845 DAEC bacteria induce expression of VEGF mRNA in T84 human epithelial cells
- 3 Antonio Celada** - Parc Científic de Barcelona, Barcelona, Spain
M-CSF-induced proliferation and LPS-dependent activation of macrophages requires Raf-1 phosphorylation to induce MKP-1 expression
- 4 Selma Essegir** - The Institute of Cancer Research, London, UK
Potential role of GDNF through GFR α -1/RET in early development of breast cancer
- 5 Isabel Fabregat** - IDIBELL-Cancer Research Institute, L'Hospitalet, Barcelona, Spain
Role of the NADPH oxidase genes (nox) in TGF-beta signalling: Implications for hepatocarcinogenesis
- 6 Angeles Garcia-Pardo** - CIB, CSIC, Madrid, Spain
Role of MMP-9 in B-chronic lymphocytic leukemia cell migration and invasion, and its regulation by alpha4beta1 integrin and CXCR4
- 7 Joan Gil** - IDIBELL-Universitat de Barcelona, Hospitalet de Llobregat, Barcelona, Spain
2-Methoxyestradiol, a superoxide dismutase inhibitor, induces VDAC-dependent apoptosis in chronic lymphocytic leukemia cells.
- 8 Gareth Jenkins** - Swansea School of Medicine, Swansea, UK
The role of Bile acids in NFkB mediated cancer progression in patients with the inflammatory condition Barrett's oesophagus.
- 9 Thomas Kuilman** - The Netherlands Cancer Institute, Amsterdam, The Netherlands
Interleukin-6 signaling is required for BRAFE600-induced senescence
- 10 Maria Julia Marinissen** - Universidad Autónoma de Madrid, Madrid, Spain
Inhibition of Heme Oxygenase-1 Interferes with the Transforming Activity of the Kaposi's Sarcoma Herpesvirus-Encoded G protein-Coupled Receptor

- I1 Eileen McNeill** - Cancer Research UK London Research Institute, London, UK
Skin Carcinogenesis in S100A9 null mice
- I2 Luis Montuenga** - Foundation for Applied Medical Research (FIMA), Pamplona, Spain
Analysis of genetic and epigenetic alterations in an inflammatory-mediated lung cancer model induced by silica
- I3 Sonia Rocha** - University of Dundee, Dundee, UK
Modulation of p53 function by IKK
- I4 Abel Sánchez-Aguilera** – CNIO, Madrid, Spain
Tumor microenvironment and mitotic checkpoint are key factors in the outcome of classical Hodgkin Lymphoma
- I5 Seng-Lai Tan** - Eli Lilly and Company, Indianapolis, USA
Role of PKC-beta enzymatic function in regulating cell survival mediated by B cell antigen receptor cross-linking
- I6 Joaquin Teixido** - CIB, CSIC, Madrid, Spain
Generation of human melanoma cell lines with stable interference or overexpression of CXCR4 and MTI-MMP for in vivo metastasis studies.

Abstracts-Sessions

Inflammation and Cancer: Crosstalk between prostaglandin and cancer signaling pathways

Raymond N. DuBois

The Vanderbilt-Ingram Cancer Center, Nashville, TN, USA

Long-term use of NSAIDs leads to a 40-50% reduction in risk for colorectal cancer. These anti-inflammatory drugs effectively target inhibition of prostaglandins by the cyclooxygenase enzymes (COX-1 and COX-2). Prostaglandins, such as PGE₂, regulate the expression of several downstream effector genes, some of which regulate pro-inflammatory pathways. These bioactive lipids signal via G protein-coupled receptors (GPCRs), which in turn can transactivate growth factor receptors and regulate cell proliferation, migration, and cell survival. Prostaglandin E (PGE₂) has been shown to directly activate components of the canonical Wnt signaling system. Additionally, PGE₂ can transactivate the epidermal growth factor receptor (EGFR) in colorectal carcinoma cells via a c-Src dependent mechanism that regulates cell proliferation and migration. We found that β -arrestin-1 may act as an important mediator in EP4 (GPCR-induced) activation of c-Src. We investigated the effects of PGE₂ on colorectal cancer cells expressing wild-type and mutant β -arrestin-1. We found that PGE₂ induces the association of an EP4 receptor/ β -arrestin-1/c-Src signaling complex resulting in the transactivation of the epidermal growth factor receptor (EGFR) and downstream Akt (PKB) signaling. The interaction of β -arrestin-1 and c-Src is critical for the regulation of colorectal carcinoma cell migration in vitro as well as metastatic spread of disease to the liver in vivo. These results show that the EP4/ β -arrestin-1/c-Src signaling complex is a crucial step in PGE₂ mediated transactivation of the EGFR and may play a pivotal role in the metastatic spread of cancer cells. Furthermore, our data implicate a functional role for β -arrestin-1 as a mediator of cellular migration and metastasis.

TLR-MyD88 dependent tissue repair response promotes intestinal tumorigenesis

Seth Rakoff-Nahoum and Ruslan Medzhitov

Howard Hughes Medical Institute and Section of Immunobiology, Yale University School of Medicine, New Haven, CT, USA

Inflammation is increasingly recognized as an important component of tumorigenesis, although the mechanisms and pathways involved are not fully characterized. One potential link between inflammation and tumor progression is through the tissue repair response. Indeed, the tissue repair program has been proposed to be fundamental to tumorigenesis, but the mechanisms responsible for triggering this program are largely unknown. Here we show that the Toll-like receptor (TLR)-MyD88 signaling pathway is involved in initiating the tissue repair response in the intestine and demonstrate a critical role for TLR signaling in tumor development. We show that MyD88 dependent signaling controls the expression of several key modifier genes of intestinal tumorigenesis and plays a critical role in tumor progression, but not tumor initiation. This study thus reveals the important role of TLR-MyD88 dependent tissue repair response in cancer progression.

Molecular cues for the development and progression of inflammation-associated liver cancer

Yinon Ben-Neriah, Ilan Stein, Rinnat M Porat, Elad Horwitz, Eithan Galun, Rinat Abramovitch and Eli Pikarsky

The Lautenberg Center for Immunology, Department of Pathology and the Goldyne Savad Institute of Gene Therapy, the Hebrew University-Hadassah Medical School, Jerusalem, Israel

Hepatocellular carcinoma (HCC) commonly develops in the background of chronic hepatitis. We have recently shown that nuclear factor- κ B (NF- κ B), a molecular hallmark of inflammatory responses that is frequently detected in tumors, links between inflammation and cancer. We ratified this hypothesis by studying Mdr2-knockout (Mdr2^{-/-}) mice, which spontaneously develops cholestatic hepatitis followed by HCC. The TNF α -NF- κ B activation axis is also upregulated in mice fed a carcinogenic choline-deficient, ethionine-supplemented diet, which also induces liver tumors on the background of chronic hepatitis. We showed that the inflammatory process triggers hepatocyte NF- κ B through upregulation of tumor necrosis factor- α (TNF α) in adjacent endothelial and inflammatory cells. To directly assess the role of hepatocyte NF- κ B in hepatocarcinogenesis, we bred Mdr2^{-/-} mice with Δ N-I κ B^{hep} mice, carrying a hepatocyte-specific inducible I κ B-super-repressor transgene, generating Mdr2^{-/-} Δ N-I κ B^{hep} mice, amenable to NF- κ B modulation. NF- κ B inhibition in Mdr2^{-/-} Δ N-I κ B^{hep} mice resulted in marked attenuation of progression to HCC mostly by promoting apoptosis of transformed cells. In addition, we observed JNK activation and cJun increased expression in Mdr2^{-/-} mice around the peak period of premalignant changes, and similarly to NF- κ B, these were dependent on TNF α signaling. Remarkably, as time elapsed, transformed cells inactivated the super-repressor transgene and started forming tumors in Mdr2^{-/-} Δ N-I κ B^{hep} mice, underscoring again the essential role of NF- κ B in HCC tumorigenesis.

It was generally thought that inflammation causes cancer by generating noxious substances that damage parenchymal cells and induce proliferation and mutations. Our findings suggest an additional mechanism: inflammation derived paracrine signals induce pro-survival intracellular pathways that cultivate cells that have acquired tumorigenic mutations, but are not yet fully transformed. We thus propose that chronic inflammation may play the role of both a carcinogen and a tumor promoter (through NF- κ B and possibly other intracellular pathways). This dual role may explain the high propensity of patients with chronic inflammation to acquire cancer compared with the low risk of acute inflammation.

Bifunctional role of PKC ζ in inflammation and cell damage

Jorge Moscat and Maria T. Diaz-Meco

Centro de Biología Molecular Severo Ochoa (CBMSO), Consejo Superior de Investigaciones Científicas, Universidad Autónoma de Madrid, Cantoblanco, Madrid, Spain

PKC ζ is important for activation of NF- κ B in several cell systems acting upstream the IKK complex in vivo and at the level of RelA phosphorylation in fibroblast cultures. We have carried out a genome-wide analysis of transcripts depending on the PKC ζ -mediated phosphorylation of the RelA S311 and have found that MDM2 appears to be a target of this novel pathway. In addition, NF- κ B is a suppressor of liver apoptosis during endotoxic shock and in T-cell mediated hepatitis. We found a reduction in ConA-induced hepatitis in PKC ζ -/- mice despite a dramatic inhibition in NF- κ B activation. This paradoxical result is explained by the fact that PKC ζ is also necessary for Jak1 activation, which is required for liver damage during T-cell mediated hepatitis. On the other hand, Par-4 is a negative regulator of PKC ζ activity and NF- κ B. Studies in Par-4-deficient mice show that its genetic inactivation leads to enhanced liver damage when injected with ConA. Par4 is a critical regulator of not only inflammation but also cancer. Thus, our results demonstrate that transformation is in most cases associated with a decrease in the levels of Par4, and that this is necessary for transformation to proceed. Recent data from our laboratory demonstrate that Par4/PKC ζ double KO mice display a normal phenotype whereas the Par-4-/- mice display enhanced tumorigenesis. These results demonstrate that PKC ζ is at least one of the bona fide physiological targets of Par-4.

A Novel Role for p120ctn in mediating inflammatory responses in skin

Mirna Perez-Moreno and Michael Davis

Howard Hughes Medical Institute Laboratory of Mammalian Cell Biology and Development. The Rockefeller University, New York, NY, USA

Although p120-catenin regulates adherens junction (AJ) stability in cultured cells, genetic studies in lower eukaryotes have not revealed a role for this protein *in vivo*. Using conditional targeting in mice, we show that p120-null neonatal epidermis exhibits reduced intercellular AJ components but not overt disruption in barrier function or intercellular adhesion. As the mice age however, they display epidermal hyperplasia and chronic inflammation, typified by hair degeneration and loss of body fat. Using skin engraftments and anti-inflammatory drugs, we show that these features are not attributable to reductions in junctional cadherins and catenins, but rather NF κ B activation. Both *in vivo* and *in vitro*, p120-null epidermal cells activate nuclear NF κ B, triggering a cascade of proinflammatory NF κ B targets. Although the underlying mechanism is likely complex, we show that p120 affects NF κ B activation and immune homeostasis in part through regulation of Rho GTPases. These findings provide important new insights into p120 function.

Differential regulation of NF-kappaB subunit function

Katie Schumm, Kirsteen J. Campbell, Sonia Rocha and Neil D. Perkins

Division of Gene Regulation and Expression, School of Life Sciences, University of Dundee, Scotland, UK

NF- κ B subunits do not regulate the same genes, in an identical manner, in all the different circumstances in which they are induced. Consequently, to learn more about its role in cancer, we have investigated the relationship between NF- κ B and the ARF/p53 tumour suppressor pathway, together with p53-independent mechanisms regulating NF- κ B function following stimulation with cytotoxic stimuli.

We find that in U-2 OS osteosarcoma cells, the chemotherapeutic drug cisplatin and the p14ARF tumor suppressor modulate the activity of RelA(p65) NF- κ B through remarkably similar mechanisms: both require ATR/Chk1 activity, induce RelA phosphorylation at Thr505 and result in NF- κ B dependent repression of Bcl-x_L expression, an anti-apoptotic gene typically induced by NF- κ B in response to inflammatory stimuli. Other chemotherapeutic drugs, such as daunorubicin, doxorubicin, mitoxantrone and etoposide, as well as DNA-damage induced by UV light, also regulate NF- κ B but have distinct effects on RelA functionality. These can include both repression and induction of anti-apoptotic genes and are independent of the ATR/ATM pathways.

In addition, we have also investigated the p52 NF- κ B subunit (NF- κ B2), which is aberrantly expressed in many tumor types. We find that endogenous p52 is a direct regulator of the Cyclin D1 promoter. However, this cannot account for all the effects of p52/p100 and we also find that p52 represses expression of the CDK inhibitor p21WAF/CIP1. However, this latter effect is dependent upon the tumor suppressor p53. By contrast, p52 co-operates with p53 to regulate other known p53 target genes. Significantly, p52 binding to these promoters results from p53-dependent recruitment. p52 can therefore define both the specificity of the p53 response as well as influence p53-regulated decision-making following DNA-damage and oncogene activation.

These results demonstrate that the NF- κ B response can vary depending on the cellular context. Understanding these mechanisms could improve both tumour diagnosis and choice of therapy.

The IKK Complex: Providing a Link between Inflammation and Cancer

Michael Karin

Laboratory of Gene Regulation and Signal Transduction, Department of Pharmacology, UCSD School of Medicine, La Jolla, CA, USA

A link between inflammation and cancer has been suspected for over two millennia, but its molecular nature remained ill defined. It has also been observed that certain bacterial (for instance *Helicobacter pylori*) and viral (for instance HBV and HCV) pathogens are major risk factors for certain types of cancer, most notably gastric and liver cancers. In trying to understand molecular mechanisms that link chronic infections and inflammation to cancer, we have postulated that transcription factor NF- κ B may be at the center of this nexus, as NF- κ B is activated in response to infection and inflammation and in turn upregulates expression of anti-apoptotic and growth promoting genes. As there are several NF- κ B transcription factors, we decided to inactivate the critical catalytic subunit of the I κ B kinase (IKK) complex, IKK β , as a way to inhibit activation of most NF- κ B forms. We used conditional gene targeting to inactivate IKK β in either cells that give rise to the malignant component of the tumor or in myeloid cells that contribute to the inflammatory infiltrate present in most tumors. Using a mouse model of colitis-associated cancer (CAC), we found that although deletion of the IKK β subunit of the IKK complex in intestinal epithelial cells does not decrease inflammation, it does lead to a dramatic decrease in tumor incidence without affecting tumor size. This effect was linked to increased epithelial apoptosis during tumor promotion. A more modest reduction in tumor number but a considerable decrease in tumor size is caused by deletion of IKK β in myeloid cells. This deletion diminishes expression of pro-inflammatory cytokines, COX-2 and MMP-9, without affecting apoptosis. These results show that the IKK/NF- κ B pathway is not only involved in suppression of apoptosis in advanced cancers but that its specific inactivation in two different cell types, one of which plays a bystander role, can attenuate formation of inflammation-associated tumors. Thus, IKK β may provide a mechanistic link between inflammation and cancer.

Using a different model, based on transplantation of a syngeneic colon carcinoma cell line (CTC26) into immunocompetent mice, we have found that the IKK/NF- κ B pathway is involved in inflammation-induced tumor progression and metastatic growth. In this case, inhibition of NF- κ B activation in the cancer cell converted inflammation-induced tumor growth to inflammation-induced tumor regression. Importantly, we found that inflammation promoted tumor growth through the induction of TNF- α , which activated NF- κ B in the cancer cell. In addition to inhibition of inflammation-induced proliferation, blocking NF- κ B in the cancer cell greatly increased sensitivity to TRAIL-induced apoptosis.

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While inflammation is a major factor that contributes to the development and progression of CAC and other inflammation-linked cancers and is estimated to be involved in up to 20% of all human cancers, we asked whether inflammation driven by NF- κ B has an important role in other forms of cancer where chronic inflammation or infection do not precede tumor development. To that end, we used a model of chemically-induced hepatocellular carcinoma (HCC) based on exposure of mice to a complete and potent carcinogen – diethyl nitrosamine (DEN). Heretofore, DEN administration, although resulting in pronounced cytotoxicity, was not found to trigger an inflammation response.

Surprisingly, mice lacking IKK β only in hepatocytes (*Ikk β Δ hep* mice) exhibited a marked increase in hepatocarcinogenesis after DEN administration. This increase correlated with enhanced reactive oxygen species (ROS) production, increased JNK activation and elevated hepatocyte death, giving rise to augmented compensatory proliferation of surviving hepatocytes. Brief oral administration of an anti-oxidant around the time of DEN exposure blocked prolonged JNK activation and compensatory proliferation and prevented excessive DEN-induced carcinogenesis in *Ikk β Δ hep* mice. A similar decrease in compensatory proliferation and hepatocarcinogenesis was observed in response to a knockout of the *Jnk1* locus. Decreased hepatocarcinogenesis was also found in mice lacking IKK β in both hepatocytes and hematopoietic-derived Kupffer cells. These mice exhibited reduced hepatocyte regeneration and diminished induction of hepatocyte growth factors, which were unaltered in *Ikk β Δ hep* mice. IKK β , therefore, orchestrates inflammatory crosstalk between hepatocytes and hematopoietic-derived cells that promotes chemical hepatocarcinogenesis. Most likely, this inflammatory response is triggered by proteins released by hepatocytes undergoing necrosis in response to DEN administration and caused activation of nearby Kupffer cells, which in turn secrete growth factors that stimulate the proliferation of surviving hepatocytes including those that acquired DEN-induced oncogenic mutation. This inflammatory response to cellular necrosis may stimulate the growth and progression of many solid cancers.

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Role of p38 α MAP kinase as an oxidative stress sensor in oncogene-induced malignant transformation

Ignacio Dolado¹, Aneta Swat¹, Ana Cuadrado¹, Nuria Ajenjo¹, Gabriella De Vita², Roberto Di Lauro² and **Angel R. Nebreda**¹

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p38 α MAP kinase is a key regulator of the cellular responses to stress that also participates in many other processes in a cell-type specific manner. A role for p38 α as a negative regulator of H-Ras-induced malignant transformation has been recently proposed, although the mechanisms involved are not fully understood. We have used p38 α -deficient cell lines to investigate the role of this signalling pathway in oncogene-driven malignant transformation. In agreement with previous studies, we found that oncogenic H-Ras expression induces a more dramatic transformed phenotype in p38 α -/- than in wild-type cells. Interestingly, p38 α is not a general inhibitor of oncogenic signalling, but seems to specifically modulate malignant transformation induced by oncogenes that produce reactive oxygen species (ROS). We found that this inhibitory effect on ROS-inducing oncogenes is due to the ability of p38 α to detect oxidative stress production early in the process of cellular transformation; this leads to p38 α activation, which in turn induces apoptosis and prevents the long-term accumulation of ROS and their carcinogenic effects. Consistent with this idea, we were able to mimic the situation of p38 α -/- cells by specifically inhibiting the ROS-induced activation of p38 α in wild-type cells, which results in increased susceptibility to oncogene-induced malignant transformation. We have also identified specific mechanisms developed by human cancer cells to uncouple ROS production from p38 α activation, leading to an enhanced tumorigenicity. However, uncoupling oncogene-induced ROS accumulation from p38 α activation results also in increased sensitive of established cancer cells to apoptosis induced by genotoxic stress. Our results indicate that oxidative stress sensing is an important mechanism for p38 α MAP kinase to negatively regulate the onset of cancer. Furthermore, in spite of its early role in cancer initiation, oxidative stress might prove beneficial for cancer treatment due to the sensitization of cells to apoptosis.

NF- κ B: a mediator of inflammatory responses and cancer

Jie Dong, Eijiro Jimi, Crystal Bussey and Sankar Ghosh

Section of Immunobiology, Yale University School of Medicine, New Haven, USA

The transcription factor NF- κ B has been linked to cancer through its roles in inflammation, cell proliferation and apoptosis. Recent studies have indicated that phosphorylation of residue Serine 276 on the p65 subunit regulates the transcriptional activity of NF- κ B. To prove the importance of posttranslational modification on the function of p65 we generated a knock-in mouse strain, in which the residue 276 on p65 was mutated from Serine to Aspartic acid to mimic constitutive phosphorylation at this site. Mice carrying this mutation are runted and develop a widespread and severe inflammatory skin disease ultimately leading to postnatal lethality 8-20 days after birth. Histological analysis reveals dramatic alterations in skin, lung and liver. This phenotype can be rescued by crossing these mice with TNFR1 knock-outs, but not IL1R knock-outs. However, the TNFR1 knockout rescued mice display developmental defects in hearts, degeneration of liver and kidney, and inflammation in liver, kidney and spleen. A number of the mice also develop tumors of liver, kidney and epithelial tissue. A majority of the TNFR1^{-/-}-p65^{S276D} KI rescued mice died between 2-10 months after birth. CHIP assays on the IL-6 and I κ B α gene promoters showed that even in resting MEFs from the KI mice, NF- κ B complexes containing the mutant p65 had a higher affinity for κ B-binding sites and recruited a greater amount of CBP and PolIII to these promoters, which might help explain the upregulation of NF- κ B target genes in these mice. Indeed, high levels of secreted TNF α was observed in liver and skin in this knock-in mouse strain. Our study therefore further establishes the biological importance of Ser276 phosphorylation on p65 function and provides a new animal model to address the link between NF- κ B, inflammation and tumorigenesis.

RelA repression of RelB activity induces selective gene activation downstream of TNFR

Emilie Jacque, Thierry Tchenio*, Guillaume Piton, Paul-Henri Romeo and **Véronique Baud**

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Tumor necrosis factor alpha (TNF α) is a potent pro-inflammatory cytokine that regulates immune and inflammatory responses and programmed cell death. TNF α stimulation causes nuclear translocation of several NF- κ B dimers, including RelA/p50 and RelB/p50. However, contrary to RelA, RelB entering the nucleus in response to TNF α cannot bind to DNA in mouse embryonic fibroblasts, strongly suggesting that RelB DNA binding activity is modulated by additional nuclear mechanisms. Here we demonstrate that TNF α promotes the association of RelA with RelB in the nucleus and that TNF α -induced RelA/RelB heterodimers do not bind to κ B sites. Remarkably, we show that RelA serine 276, the phosphorylation of which is induced by TNFR ligation, is crucial for RelA/RelB complex formation and subsequent inhibition of RelB DNA binding. In absence of RelA phosphorylation on serine 276, TNF α stimulation leads to a strong increase in the expression of endogenous NF- κ B responsive genes, such as Bcl-xL, whose transcriptional up-regulation is mainly controlled by RelB. Our findings demonstrate that RelA has a major regulatory role serving to dampen RelB activity in response to TNF α , and define a new mechanism that represents an essential step leading to selective NF- κ B target gene expression.

NF- κ B as a Potential Therapeutic Target for Malignant Melanoma

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The pathogenesis of many known cancers, including a good percentage of malignant melanomas, has been documented to be associated with aberrant activity of I κ B kinase (IKK). Whether IKK is able to serve as a therapeutic target in melanoma is unknown. We have shown that inhibition of NF- κ B by expression of a super repressor form of I κ B or by ribozyme knock down of IKK-beta, slows melanoma tumor growth. We also have shown that inhibition of constitutive IKK activity by the novel compound BMS-345541, a highly selectively inhibitor of IKK-beta, reduces constitutive NF- κ B activity, reduces CXCL1 chemokine secretion by cultured melanoma cells, reduces growth of human melanoma cells in vitro and reduces the growth of human melanoma tumors in vivo. The BMS-345541 inhibition of tumor cell growth is through mitochondria-mediated apoptosis, based on release of apoptosis-inducing factor (AIF), dissipation of mitochondrial membrane potential and reduced ratio of Bcl-2/Bax in mitochondria. The BMS-345541 execution of apoptosis is AIF dependent but largely caspase independent. Our studies suggest that BMS-345541 mediated IKK inhibition results in mitochondria-mediated apoptosis of tumor cells since the programmed death machinery-mitochondria in melanoma cells is greatly regulated by NF- κ B signaling. Therefore IKK may serve as a target for melanoma therapy.

Unique Features of the Death Induced Signaling Complex in Hepatocytes Exposed to TNF

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TNF can activate both pro-inflammatory and apoptotic signaling pathways in cells. In hepatocytes, TNF typically leads to pro-inflammatory signaling. In the setting of sensitizing agents such as actinomycin D, TNF exposure leads to apoptosis in hepatocytes. We have previously shown that nitric oxide limits TNF induced apoptotic signaling through the inhibition of the death-induced signaling complex (DISC). This occurs through cGMP-dependent and -independent mechanisms. The independent mechanisms include the s-nitrosation of caspases. Further exploration of TNF signaling in hepatocytes revealed numerous unique aspects of DISC formation. We have shown that exposure to actinomycin D alone or actinomycin D plus TNF leads to a dramatic increase in study-state FAS associated death domain protein (FADD) levels. This occurs through a caspase-8 dependent mechanism and involves increases in unphosphorylated FADD levels. Furthermore, exposure to TNF or actinomycin D alone leads to the interaction of TNF receptor with DISC components with uptake into multiple intracellular compartments. The combination of TNF with actinomycin D amplifies the formation of the DISC with even greater trafficking of the DISC into these intracellular compartments. These unique features of DISC formation in hepatocytes will be discussed.

Chemokines and Cancer Progression

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Chemokines are chemotactic cytokines classically involved in immune system homeostasis and inflammation. In recent years, chemokines have also been shown to be key regulators of tumor-stroma communication, although their function in cancer progression is complex and poorly understood. Chemokines may act on tumor and stromal cells by (a) promoting proliferation or survival of neoplastic cells, (b) increasing the metastatic potential of these cells, (c) controlling tumor angiogenesis, (d) directing tumor infiltration by hematopoietic cells, and (e) regulating tumor immune response. There is strong evidence that some chemokine-chemokine receptor pairs, such as CXCL12/CXCR4, promote tumor progression. Nonetheless, evidence suggests that other chemokine receptors, such as CCR5 and its ligands (CCL3, CCL4, CCL5 and CCL8), may promote either cancer growth or regression. We found that CCR5 activation in breast cancer cell lines induced transcriptional activity of the p53 tumor suppressor gene. This CCR5-p53 pathway appears to be relevant for breast cancer progression in humans. Indeed, breast cancer patients carrying the *ccr5*Δ32 polymorphism, which renders a non-functional receptor, have a higher relapse frequency and shorter disease-free survival than patients carrying wild type *ccr5* alleles; this effect was observed only in those individuals with non-mutated p53 tumors. In addition, tumors from *ccr5*Δ32 patients showed decreased lymphocyte infiltration compared to those from *ccr5* wild type individuals, suggesting a role for this receptor in tumor-stroma communication. Interestingly, CCR5 expressed on T lymphocytes concentrated at the immunological synapse during antigen presentation. Accumulation of CCR5 at the synapse rendered T cells less sensitive to chemotactic gradients, thus increasing the stable interaction between T cells and antigen-presenting cells. The consequence of this accumulation is that CCR5 acted as a co-stimulatory receptor for T cells, enhancing T cell-mediated immune responses. Concurring with these data, tumors grew more rapidly in CCR5^{-/-} mice than in CCR5^{+/+} littermates. CCR5 crosstalk with other chemokine-chemokine receptor pairs in the tumor environment will be discussed.

Inflammation, Proteolysis and Cancer

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The main function of the mammalian immune system is to monitor tissue homeostasis and protect against invading or infectious pathogens and to eliminate damaged cells; thus, it is surprising that cancer occurs with such a high frequency in humans. Recent insights gained from clinical studies and experimental mouse models of carcinogenesis expand our understanding of the complex relationship between immune cells and developing tumors. This presentation will discuss the paradoxical role of adaptive and innate leukocytes as critical regulators of cancer development based upon recent insights gained by manipulating immune responses in mouse models of de novo and spontaneous tumorigenesis.

Role of CD11b Positive Immature Myeloid Cells in Tumor Promotion and Eradication

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It has been known for decades that granulocytosis in the peripheral blood and infiltration of granulocytes and myeloid cells into tumors occurs in the large majority of human and experimental cancers. These cells predominantly express Ly-6G (Gr1) and the increase in these cells is concomitant with cancer progression and metastasis. In 1995, it was then shown by us that Gr1⁺ cells have a functional role in tumor growth. Furthermore, it was established that the Gr1⁺ cells were part of a paracrine stimulatory loop that was acquired by cancer cells as they progressed to higher degrees of malignancy. Thus, it was shown that anti-Gr1 treatment could slow down tumor growth in T cells deficient mice. In addition, elimination of Gr1⁺ cells in the tumor-bearing euthymic host resulted in T cell-mediated tumor rejection, consistent with the notion that these myeloid cells in the tumor-bearing host suppressed tumor immunity. These studies have been confirmed and extended by numerous investigators in subsequent years. Furthermore, it was shown that the Gr1⁺ myeloid cells promoted B cell responses and that antibodies to the developing tumors promoted tumor growth. There is also overwhelming evidence that these myeloid cells are essential for tumor angiogenesis and growth. Thus, multiple lines of evidence imply the tumor-promoting immunosuppressive role of Gr1⁺ CD11b⁺ FcR2/III⁺ myeloid cells in cancer. Like other CD11b⁺ stromal cells, these cells pick up antigen released from the cancer cells into the tumor stroma. Therefore, tumor-specific T cells can lyse these CD11b⁺ stromal cells, thereby causing significant destruction of tumor stroma. Importantly, we found that targeting the tumor stroma as well as the cancer cells is essential for achieving recurrence-free destruction of large solid tumors. Thus T cell-resistant cancer cells can be eliminated as “bystanders” in the tumor stroma. Importantly, bone-marrow-derived as well as non-bone marrow-derived stromal cells must be targeted, and the exact mechanism whereby the resistant variant cancer cells are eliminated is being currently investigated.

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MT1-MMP and inflammation: MT1-MMP is involved in chemokine- and nitric oxide -induced angiogenesis and in monocyte migration

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Cancer development involves the transformation and invasion of tumor cells but also angiogenic and inflammatory responses. Matrix metalloproteinases (MMPs), and in particular MT1-MMP, are important for tumor cell invasion. We have characterized the regulation and function of MT1-MMP during angiogenesis (Gálvez et al, 2001, 2002, 2004, 2005). More recently, we have aimed at exploring MT1-MMP role in the inflammatory context. We have explored: 1) the function of MT1-MMP in the angiogenesis induced by inflammatory mediators; and 2) the function of MT1-MMP in leukocyte recruitment. Both human and mouse models have been employed. We have demonstrated that MT1-MMP is required for chemokine CCL2(MCP-1)- but not CXCL12(SDF-1)-induced angiogenesis; in fact, CCL2 regulates MT1-MMP activity by modulating its dimerization (Gálvez et al., 2005). Nitric oxide also requires the presence and the activity of MT1-MMP to induce efficient endothelial migration and formation of capillaries; moreover, nitric oxide regulates MT1-MMP expression, activity, and function in human and mouse endothelial cells (Genís et al., 2006). Finally, MT1-MMP is important for CCL2-induced migration of human monocytes on fibronectin and endothelial ligands and for their transmigration through activated endothelial cells (Matías-Román et al., 2005); in this regard, CCL2 increases endothelial transmigration of splenocytes from wildtype but not from MT1-MMP-null mice. In summary, MT1-MMP is relevant for proper inflammatory responses since it is required for both chemokine- and nitric oxide-induced angiogenesis as well as for monocyte migration. Further analysis of the in vivo function of MT1-MMP in the inflammatory context will provide valuable information to consider this protease as a novel target for therapy in inflammation-related processes including cancer.

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Risk benefit considerations regarding NSAIDs as anticancer agents

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Randomized trials have proven that a number of selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs) can suppress the recurrence of colorectal adenomatous polyps. However, prevention of colorectal neoplasia alone cannot justify NSAID use (except for suppression of polyps among individuals with Familial Adenomatous Polyposis). Aspirin is unique among NSAIDs because it reduces risk of coronary heart disease and other thrombotic events, making it an attractive candidate for application to cancer prevention. In observational epidemiologic studies, aspirin use has been consistently associated with lower risk of colorectal cancer, and some observational studies have suggested that aspirin use may also be associated with lower risk of certain other cancers including cancers of stomach, esophagus, breast, prostate, and lung.

We examined the association between daily use of adult aspirin (>325 mg) and the incidence of all cancers combined, as well as incidence of the most common cancer sites, in the CPS-II Nutrition Cohort, a prospective study begun by the American Cancer Society in 1992/93. Analyses were based on nearly 18,000 incident cancers identified among approximately 145,000 men and women during ten years of follow-up. Compared to taking no aspirin, taking at least one adult aspirin (>325 mg) daily for at least five years was associated with an approximately 15 percent lower incidence rate of all cancers combined, although this association was not formally statistically significant among women (among men, multivariate adjusted hazard ratio HR= 0.84, 95% CI = 0.76, 0.93, among women, multivariate adjusted hazard ratio HR= 0.86, 95% CI = 0.72, 1.02). Most of the inverse association with overall cancer incidence was attributable to prostate cancer in men (HR=0.81, 95% CI=0.70, 0.95), breast cancer in women (HR=0.82, 95% CI=0.62, 1.08), and colorectal cancer in both sexes (HR=0.69, 95% CI=0.52, 0.91), although the association with breast cancer was not statistically significant. No association was observed between daily use of adult aspirin for five or more years and lung cancer incidence (HR=0.97, 95% CI=0.75, 1.24). Neither daily use of adult aspirin for less than five years, nor daily use of “baby” aspirin (typically 81 mg) for at least five years, was associated with overall cancer incidence, although statistical power to examine long-term baby aspirin use was limited.

An important consideration for any potential anticancer agent is cardiovascular safety. While aspirin is known to reduce risk of coronary heart disease, the relationship between use of traditional NSAIDs (tNSAIDs), other than aspirin, and coronary heart disease remains unclear. Preliminary analyses in the CPS-II Nutrition Cohort suggest modestly increased risk of coronary heart disease (fatal coronary heart disease or nonfatal myocardial

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infarction) among persons using high levels of tNSAIDs, although these associations were not always statistically significant. Any cardiovascular toxicity of non-aspirin NSAIDs would greatly limit their use for cancer prevention.

If it were proven to be causal, the inverse association that we observed between aspirin use (> 325 mg daily for five or more years) and overall cancer incidence would have important implications with respect to clinical recommendations about who should be using aspirin and at what dose. Prophylactic use of aspirin is currently recommended only for the primary and secondary prevention of cardiovascular events in high risk populations. More evidence is needed about the relationship between long-term regular use of adult dose aspirin and risk of cancer.

How to influence people: The changing repertoires of *Helicobacter pylori*

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Substantial evidence indicates that *H. pylori* has been a colonizer of the human stomach since the earliest human populations. There also is much evidence that it co-evolved with humans to inhabit the gastric niche. *H. pylori* is a highly diverse organism and the diversity is central to a biology of intraspecies cooperation and competition. In particular, *H. pylori* uses non-randomly distributed repetitive DNA sequences in its genome to create phenotypic variation. *H. pylori* also has stereotypic means for signaling the host. In this presentation, I emphasize *H. pylori* signals that affect epithelial cell cycle. The interaction is well-choreographed, but the *H. pylori* actors are subject to variation through repetitive DNA that affects important host phenotypes. The interactions can best be explained by a dynamic model of interactions involving negative feedback and differential host-based selection of bacterial populations. While germane to *H. pylori*, an important player in gastric oncogenesis, the model also is adaptable to other persistent co-evolved organisms at mucosal interfaces.

Chronic pancreatitis and K-ras oncogenes are required to induce pancreatic ductal adenocarcinoma in adult mice

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Pancreatic ductal adenocarcinoma (PDA) is the most deadly form of human cancer. After diagnosis, just 3% of cases survive more than 5 years and surgical patients frequently die within twelve months. During the last few years, the molecular events responsible for PDA have been unveiled. K-Ras is the most frequently mutated oncogene, found in more than 90% of the cases (1). Other frequent mutations involve deletion of the cell cycle inhibitor p16INK4a, and inactivation of P53 and Smad4 (2). In mice, Hingorani et al., have shown that expression of an endogenous K-RasD12 oncogene in all pancreatic lineages since early embryonic development (E8.5) results in the formation of preneoplastic intraepithelial lesions (mPanIN) and PDA histologically indistinguishable from those found in human patients (3). In contrast, specific expression of K-Ras oncogenes in either acinar or ductal cells does not lead to the formation of mPanINs or PDA, thus suggesting that PDA may originate from stem or progenitor cells (4). In our laboratory, we have crossed our conditional K-RasV12 strain (5) with *Elastase-tTA*; *tetO-PhCMV-Cre* transgenic mice (6) to generate compound mice in which we can turn on expression of K-RasV12 in the acinar lineage at any time since embryonic day 16.5 (E16.5). Expression of K-RasV12 during late embryonic development also results in the appearance of frequent mPanINs and PDA. Yet, susceptibility to K-RasV12 induced-mPanINs and PDA decreases dramatically during postnatal development to completely disappear in adulthood. These observations suggest that the number of putative stem/progenitor cells susceptible to transformation by K-Ras oncogenes decreases during postnatal development and no longer exist (or are drastically reduced) in adult mice. Since human PDA is not a pediatric tumor, we have investigated whether we could recapitulate this disease in adult mice in order to generate a truly meaningful model system for human PDA, beyond molecular (K-Ras oncogenes) and anatomopathological (PanINs) similarities. To this end, we have treated 30 days old mice (P30) with caerulein, a cholecystokinin analogue that induces chronic pancreatitis. This treatment, by itself, does not lead to mPanINs or PDA for at least 12 months. However, expression of the resident K-RasV12 oncogene at P60, that is 30 days after the onset of pancreatitis, leads to high numbers of mPanIN lesions that rapidly progress to PDA. Similar results have been observed if caerulein treatment is provided to mice that already express the K-RasV12 oncogene. These observations suggest that adult mice maintain a small pool of permissive stem/progenitor cells that becomes amplified as a consequence of the damage caused by pancreatitis, including an innate and adaptive inflammatory process. Identification of these putative cells should help to

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elucidate the mechanisms responsible for the development of human PDA and to understand how chronic lesions create the necessary environment to support tumor formation. Moreover, we hope that animal models that closely recapitulate human neoplasias will help to better evaluate preventive as well as therapeutic strategies that may benefit cancer patients.

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The dynamics of the inflammatory response to cancer

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In 1863, Virchow hypothesized that the cancer originated at sites of chronic tissue injury and that the ensuing inflammation they cause enhances cell proliferation. While it is now clear that proliferation of cells alone does not cause cancer, sustained cell proliferation in an environment rich in inflammatory cells, growth factors, activated stroma, and DNA damage promoting agents, certainly potentiates and/or promotes neoplastic risk. The causal relationship between inflammation, innate immunity and cancer is now widely accepted. Indeed, modifying the inflammatory response decreases tumor development and progression. We used genetic and in vivo imaging techniques to study the interaction between leukocytes and epithelial cancer cells during tumor progression by crossing transgenic tumor-prone mice with mice expressing enhanced green fluorescent protein under general and inflammatory cell-specific promoters and with mice lacking specific matrix metalloproteinases (MMPs). We visualized the behavior of the cancer cells and leukocytes in living, anaesthetized mice using a novel four-color spinning disk confocal microscope. We found that developing tumors undergo an inflammatory switch. The leukocytes observed at the tumor-stroma interface are very motile whereas those within the tumor are relatively immotile. The motility of the inflammatory cells is regulated by hypoxia and phagocytosis. These studies show the dynamic behavior and interactions of cancer cells and leukocytes during mammary carcinoma progression. Our data support the hypothesis that that inflammatory cells both enhance tumor growth or inhibit tumor progression. The challenge is to determine which cellular interactions are pro-tumor, and thus should be inhibited, and which ones inhibit tumors and should be enhanced.

Protection against oxidant and inflammatory stress: the role of inducers of the Phase 2 response

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The steady increase in the number of new cancer cases diagnosed each year and the disappointingly slow progress in the successful treatment of common solid tumors highlights the urgent need for the development of strategies for prevention. Such focus is becoming especially important now as we are experiencing an increase in the environmental toxic burden and aging of world populations. Essential for the defense of mammalian cells and organisms against the toxicities of electrophiles and oxidants is the family of phase 2 enzymes. These proteins are normally expressed at basal levels, however under conditions of electrophile or oxidative stress, their gene expression is markedly elevated providing a diverse and highly reliable battery that detoxifies the toxic agents and ultimately enables the cell to overcome the challenge and survive. Phase 2 enzymes are coordinately inducible by a variety of agents and this induction is now widely recognized as a promising strategy for protection against cancer. Inducers react with specific cysteine sulfhydryl groups of the sensor protein Keap1, thereby allowing transcription factor Nrf2 to translocate to the nucleus and activate transcription through the antioxidant response element (ARE), an enhancer upstream regulatory element that is present on phase 2 genes.

Interestingly, phase 2 inducers are also anti-inflammatory, e.g., they suppress the γ -interferon-induced gene expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase 2 (COX-2), and these responses also depend on the same cellular components (i. e., Keap1 and Nrf2) that are essential for induction of phase 2 enzymes. Importantly, nitric oxide and 15-deoxy- $\Delta^{12,14}$ -prostaglandin J₂, products of iNOS and COX-2 enzyme activities, respectively, have been shown to react with Keap1 and induce phase 2 enzymes indicating that induction of the phase 2 response may serve as a feedback mechanism to protect against chronic inflammation. The anti-inflammatory and phase 2 inducer properties are common to inducers of vastly different architecture, among them plant isothiocyanates, curcuminoids, as well as synthetic oleanolic acid-derived triterpenoids. A detailed structure-activity relation study within the triterpenoid series revealed that their potencies in inducing phase 2 enzymes correlates linearly over 5 orders of magnitude of concentrations with their potencies in inhibiting pro-inflammatory responses. This remarkable correlation strongly suggests that these processes must be mechanistically related.

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The isothiocyanate sulforaphane, that was isolated as the principal and very potent phase 2 inducer from broccoli, has been subsequently demonstrated to inhibit tumor development in at least eight different animal models. Recently, in a model of UV light-induced skin carcinogenesis in SKH-I hairless mice, topical or dietary administration of broccoli sprout extracts as a source of sulforaphane inhibited tumor incidence, multiplicity, and total tumor burden. In addition, sulforaphane protects against a number of non-neoplastic conditions in animal cells or models, e.g., *Helicobacter pylori* infection, hypertension, atherosclerosis, cerebral ischemia, and photooxidative damage of the retina. Thus, studies with sulforaphane have exemplified “proof of concept” that inducing the phase 2 response is a powerful strategy for protecting against cancer and other chronic diseases in the development of which xenobiotic challenge, oxidative stress, inflammation, and radiation have been implicated.

Bombesin induces cyclooxygenase-2 expression and migration in the human colon adenocarcinoma

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Cyclooxygenase-2 (COX-2), the gastrin-release peptide (GRP) and its cognate receptor (GRP-R) are overexpressed in colorectal carcinomas and are associated with cell growth, invasiveness and tumor progression. However, a molecular link between all of them in adenocarcinomas has not been established. We found that bombesin (BBS), a GRP homologue, stimulates the expression of COX-2 mRNA and protein in human colon adenocarcinoma Caco-2 cells, resulting in enhanced release of prostaglandin E2 (PGE2). These effects were markedly inhibited by the specific BBS antagonist RC-3940-II. BBS promotes the activation of the nuclear factor of activated T cells (NFAT) through a Ca^{2+} /calcineurin (Cn)-linked pathway. Upon BBS stimulation, the NFATc1 isoform translocates into the nucleus with a concomitant increase in NFATc1 binding to two specific recognition sites in the promoter region of the COX-2 gene. Furthermore, inhibition of Cn activity by the immunosuppressive drug Cyclosporin A (CsA) impaired NFAT activation and diminished COX-2 expression in BBS-stimulated cells. Interestingly, BBS pretreatment strongly enhances the invasive capacity of Caco-2 cells, effect which was inhibited by a COX-2 specific inhibitor. Similarly, tumor promoter agents also induce Cox-2 in Caco 2 cells via NFAT and inhibition of this induction results in decreased colony formation ability. In addition, we have used retroviral-mediated transfer of Cox-2, a dominant negative NFAT and active Calcineurin in those cells, which are able to strongly modified the growth and migration of carcinoma cells. These findings provide the first evidence for the involvement of the Ca^{2+} /Cn/NFAT pathway in BBS-mediated induction of genes involved in colon carcinoma invasiveness such as COX-2.

Potential role of liver microenvironment in metastasis and recurrence of hepatocellular carcinoma

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Hepatocellular carcinoma (HCC) is an aggressive malignant tumor worldwide with a dismal outcome, mainly due to metastases or post-surgical recurrence. Since metastases may be influenced by permissive target environments, the role of the liver microenvironment in metastasis was analyzed by cDNA expression profiling (9180 genes) of noncancerous hepatic tissues from 20 HCC resection patients with or without portal vein metastases. Supervised methods uncovered a unique 454 gene expression profile largely contributed by inflammation/immune responses that could significantly discriminate ($p < 0.001$) noncancerous hepatic tissues from HCC patients with or without portal vein metastases during cross-validation ($p < 0.05$). This signature, whose lead genes indicate a major contribution of certain immune cells, is principally different from the prognostic signature in metastatic HCC specimens. A global Th1 and Th2-like cytokine shift occurs in hepatic metastatic HCC tissues and is accompanied by expression changes in macrophage colony stimulating factor (CSF1) and nitric oxide synthase 2. A refined immune response-related 17-gene signature was then monitored in 115 HCC patients by quantitative real-time polymerase-chain-reaction analyses with training and independent validation. This refined signature was a superior predictor of HCC metastatic potential or recurrence using only noncancerous hepatic tissues (>93% and 79% overall prediction accuracy for survival or recurrence respectively), independent of other known prognostic clinical variables. In summary, a unique immune responsive 17-gene signature was validated as a predictive tool to determine HCC metastatic potential using only noncancerous hepatic tissues. Thus, this predictor may have potential utility in clinical settings to classify patients with HCC metastatic potential.

Tumor suppression, senescence and aging

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The INK4/ARF locus encodes three tumour suppressors, namely, p15INK4b, ARF, and p16INK4a, and is among the most frequently inactivated loci in human cancer. Our current understanding of the function of this locus indicates that this locus is a sensor of “oncogenic stress” that is activated by the presence of oncogenes. Upon activation, the proteins encoded by the INK4/ARF locus activate either senescence or apoptosis. During this past year we have made progress both in the characterization of senescence and in the analysis of the INK4/ARF locus.

Oncogene-Induced Senescence (OIS) is considered among the most important cellular responses against tumor progression. Until now, however, the analysis of OIS had been restricted to *in vitro* cultured cells subjected to high ectopic expression of oncogenes. To address the existence of OIS in a relevant setting of oncogene-driven tumorigenesis, we have identified new molecular markers for OIS using DNA microarrays (ref. 1). We have obtained robust molecular markers for OIS and we have focused in three of them, namely, Dec1, DcR2 and p15Ink4b. These *de novo* markers have been complemented with tumor suppressors involved in *in vitro* OIS, such as p16Ink4a and p19Arf, and with other markers of *in vitro* OIS, such as senescence-associated β -galactosidase (SA β Gal) and senescence-associated heterochromatin foci (SAHF). All these markers have been tested *in vivo* using an inducible knock-in K-rasV12 mouse developed by Mariano Barbacid and colleagues. These mice develop pre-malignant and malignant lesions driven by the activation of an endogenous K-ras oncogenic allele. Using this system, we have found that pre-malignant lesions (adenomas) in lung and pancreas are positive for all the above-mentioned markers, whereas malignant lesions (carcinomas) are negative. We conclude that senescent cells are a defining feature of pre-malignant tumours, while OIS is absent in malignant tumours. The evaluation of OIS in tumours could be valuable in the diagnosis and/or prognosis of cancer.

Little is known about the mechanisms that govern the expression of the INK4/ARF locus. We have recently identified a DNA replication origin at the INK4/ARF locus that assembles a multiprotein complex containing Cdc6, Orc2, and MCMs, and that coincides with a conserved non-coding DNA element, also called Regulatory Domain (RD) (ref. 2). Targeted and localized RNAi-induced heterochromatinization of RD results in transcriptional repression of the locus, thus indicating that RD is a relevant transcriptional regulatory element. In a first approximation, we have perturbed the function of RD by overexpressing Cdc6, which is known to bind RD and

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also has been proposed to possess oncogenic activity. We have found that high levels of Cdc6 result in RD-dependent transcriptional repression, recruitment of histone deacetylases and heterochromatinization of the INK4/ARF locus, and concomitant decrease in the expression of the three tumour suppressors encoded by this locus. In agreement with its ability to repress the INK4/ARF locus, Cdc6 displays cellular immortalization activity and neoplastic transformation capacity in cooperation with oncogenic Ras. Finally, human lung carcinomas with high levels of Cdc6 are associated with low levels of p16INK4a. We conclude that aberrant expression of Cdc6 is oncogenic by directly repressing the INK4/ARF locus through the RDINK4/ARF element.

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Functions of the transcription factor AP-1(Fos/Jun) in colitis-associated cancer

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The dimeric transcription factor AP-1 (activating protein-1) exerts diverse biological functions including cell proliferation, survival, differentiation and transformation. Increasing evidence suggests that signalling through AP-1 may provide a link between chronic inflammation and cancer. Here, we have addressed the functions of the AP-1 components c-Jun and Fra-1 in colitis-associated cancer (CAC), as both proteins are frequently over-expressed in human colorectal cancer. CAC was induced by azoxymethane/dextrane sulphate sodium (DSS) and preliminary studies in wild-type mice revealed a strong expression of c-Jun in both, tumors and infiltrating immune cells. However, tumor number and size as well as the severity of DSS-induced colitis were not affected in mice with conditional deletion of c-Jun in the intestinal epithelium. Moreover, tumor formation was also not affected by deletion of JNK-1, a central regulator of c-Jun activity. These findings suggest that the JNK-1/c-Jun pathway is apparently dispensable for the formation of CAC, which contrasts recent observations that c-Jun is essential for intestinal neoplasia in APC^{min} mice (Nateri et al., 2005, Nature 437:281-5). However, we found that the Fos family member Fra-1 was required for the oncogenic functions of AP-1 in CAC, since tumor burden was approx. threefold decreased in the absence of Fra-1. Although the underlying molecular mechanism remains to be determined, we will next investigate which dimerising partner is employed by Fra-1 to define the AP-1 dimer composition controlling intestinal inflammation and carcinogenesis.

Regulation by Nrf2-Keap1 System of Cellular Defense Mechanisms against Electrophiles and Carcinogenesis

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Biotransformation process of xenobiotics is usually divided into two consecutive reactions. Phase I reaction is mediated by cytochrome P450 systems, while Phase II enzymes promote conjugation of Phase I products with various hydrophilic moieties. Characterization of the regulatory elements of Phase II detoxifying enzyme genes revealed that electrophiles transcriptionally activate the expression of these genes through the antioxidant/electrophile responsive element (ARE/EpRE). Studies on the regulation of erythroid-specific gene expression originally identified the NF-E2 binding motif and the CNC family of transcription factors. The NF-E2 motif and ARE share high-level sequence similarity, suggesting that one of the CNC family members may activate transcription through ARE. Of the CNC factors, Nrf2 is expressed in metabolic and detoxification organs, such as liver, kidney and intestine, and in organs continuously exposed to the environment, such as skin, lung and digestive tract. It was therefore assumed that Nrf2 acts as a transcriptional activator interacting with ARE. Targeted disruption of the mouse *nrf2* gene revealed that Nrf2 is essential for the coordinated induction of the defense enzymes. Detailed analysis of the regulatory mechanisms governing Nrf2 activity led to the identification of a new protein, Keap1, which represses Nrf2 activity by binding to the N-terminal Neh2 domain. Electrophiles liberate Nrf2 from the repression by Keap1 and provoke the nuclear accumulation of Nrf2, suggesting that the Nrf2-Keap1 system acts as a sensor for xenobiotics and oxidative stress. Targeted disruption of the mouse *keap1* gene induced constitutive expression of Nrf2-target genes in the Keap1-deficient mouse. Nrf2 turns over rapidly through the proteasome pathway, whereas electrophiles stabilize Nrf2. These results support the contention that Keap1 regulates the rapid proteolysis of Nrf2 and this process provides an important basis for the tight regulation of cellular defense enzymes by Nrf2.

Microenvironment and Cancer: Inflammation and MicroRNA

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Free radicals are ubiquitous in our body and are generated by normal physiological processes, including aerobic metabolism and inflammatory responses, to eliminate invading pathogenic microorganisms. Because free radicals can also inflict cellular damage, several defenses have evolved both to protect our cells from radicals—such as the p53 pathway and antioxidant scavengers and enzymes—and to repair DNA damage. Free radicals can cause an adaptive increase in certain of the protective base excision repair enzymes. Paradoxically, if the increase in enzymes is imbalanced, e.g., the DNA glycosylase is increased more than the apurinic endonuclease, frameshift mutations occur as a novel etiology of microsatellite instability. Understanding the relationship between chronic inflammation and cancer provides insights into the molecular mechanisms involved. In particular, we highlight the interaction between nitric oxide and p53 as a crucial pathway in inflammatory-mediated carcinogenesis.

MicroRNA (miRNA) expression profiles for lung cancers were examined to investigate the miRNA involvement in lung carcinogenesis. miRNA microarray analysis identified statistical unique profiles, which could discriminate lung cancers from noncancerous lung tissues as well as molecular signature that differ in tumor histology. miRNA expression profiles correlated with survival of lung adenocarcinomas including those classified as disease stage I. High hsa-mir-155 and low hsa-let-7a-2 expression correlated with poor survival by univariate analysis as well as multivariate analysis for hsa-mir-155. The miRNA expression signature on outcome was confirmed by real-time RT-PCR analysis of precursor miRNAs and cross-validated with an independent set of adenocarcinomas. These results indicate that miRNA expression profiles are new class of diagnostic and prognostic markers of lung cancer.

Abstracts-Posters

1 p21(WAF1/CIP1) regulates the NF-κB-dependent macrophage activation pathway and suppresses septic shock induction

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p21 is an S-phase cell cycle inhibitor that regulates development of tumors and of lupus autoimmunity. Here we provide evidence for a novel role for p21 as a negative regulator of macrophage activation by the nuclear factor-kappa B (NF-κB) pathway and of septic shock. This property of p21 is unrelated to its cell cycle inhibitory activity. The absence of p21 caused accelerated and prolonged NF-κB promoter activity following macrophage stimulation by lipopolysaccharide (LPS). p21 regulation of NF-κB activity involved the NF-κB inhibitor IκBa, since p21 deficiency led to decreased IκBa levels following activation. p21 regulation of NF-κB is also critical for progression of in vivo inflammation, since p21^{-/-} mice showed increased sensitivity to LPS-induced septic shock. p21^{-/-} mice produced high TNF-α but low IL-10 levels and developed lethal septic shock following delivery of LPS doses that were sublethal in controls. These data suggest that p21 attenuates macrophage activation and contributes to a balanced innate immune response to inflammatory stimuli. Overall, our findings project a role for p21 in the control of NF-κB-associated inflammation and suggest that modulation of p21 expression levels could be considered for the treatment of inflammation-associated diseases.

2 CI845 DAEC bacteria induce expression of VEGF mRNA in T84 human epithelial cells

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Chronic inflammatory disorders of the gastrointestinal tract facilitate intestinal carcinoma progression. Inappropriate immunological responses against bacteria have been suggested to be involved in such disorders. Amongst these bacteria, diffusely adhering Escherichia coli (DAEC) strains have been isolated from patients with active Crohn's disease. CI845 strain of DAEC, which harbors the fimbrial F1845 adhesin interacts with the human intestinal cell line T84 via the decay-accelerating factor (DAF or CD55) and CEA-related cell adhesion molecules (CEACAMs). We report here that the CI845 bacteria induce increase of Vascular Endothelial Growth Factor (VEGF) expression in T84 cells. This increase is time and dose dependent and requires the binding to the DAF receptor. The increase of VEGF mRNA expression is inhibited by Emetin, an inhibitor of transcription. Extracellular Regulated Kinases-induced signalling pathways are implicated in this effect since the U0 inhibitor completely blocks the increase of VEGF mRNA expression whereas the AKT- and PKC-dependant pathways are necessary but not sufficient. Upstream of these pathways a Src protein kinase is involved since the PP2 inhibitor blocks the activation of ERK and AKT and inhibits the increase of VEGF mRNA expression. We are currently assaying the production of VEGF protein in this cell system and checking that VEGF produced by infected T84 cells is able to induce vessels formation in an angiogenesis model by using Embryonic stem cells differentiation.

3 M-CSF-induced proliferation and LPS-dependent activation of macrophages requires Raf-1 phosphorylation to induce MKP-1 expression

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Macrophages are key regulators of immune responses. In the absence of an activating signal, murine bone marrow-derived macrophages undergo proliferation in response to their specific growth factor, namely M-CSF. The addition of bacterial LPS results in macrophage growth arrest and their engagement in a pro-inflammatory response. Although participation of ERKs is required for both macrophage proliferation and activation, ERK phosphorylation follows a more delayed pattern in response to activating agents. In primary macrophages, MAP kinase phosphatases (MKP)-1 is a key regulator of the time-course of MAPK activity. Here we showed that MKP-1 expression is dependent on Raf-1 activation. The time-course of Raf-1 activation correlated with that of ERK-1/2. However, while ERK phosphorylation in response to M-CSF is Raf-1-dependent, in response to LPS an alternative pathway directs the activation of these kinases. Inhibition of Raf-1 activity increased the expression of cyclin-dependent kinase inhibitors and growth arrest. In contrast, no effect was observed in the expression of pro-inflammatory cytokines and inducible nitric oxide synthase following LPS stimulation. The data reported here reveal new insights into how signaling determines opposing macrophage functions.

4 Potential role of GDNF through GFRalpha-I/RET in early development of breast cancer

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A signal-trap library of transcripts overexpressed in invasive breast tumour cells compared to normal tissue was generated to identify proteins that are involved in epithelial cell migration and invasion of the extracellular matrix. Our screen identified the cell surface GFRalpha-I (GDNF family receptor alpha-I) to be overexpressed in breast tumours and analysis of GFRalpha-I expression on a breast tumour tissue array from patients with invasive breast carcinoma showed that its expression correlates with tumours with lympho-vascular invasion and a positive estrogen receptor status.

GFRA-I is a receptor of GDNF (glial-cell-derived neurotrophic factor) and upon ligand binding forms a complex with the tyrosine kinase receptor RET and signals to promote cell survival, proliferation and migration. GDNF expression in macrophages and microglia following an inflammatory stimulation has been shown as well as the ability of GDNF to modulate TNF turnover in immune cells at the post-transcriptional level. We have shown by in vitro assays that GDNF, through GFRalpha-I, stimulates the survival, proliferation and scattering of a breast cancer cell line. We are currently investigating the regulation of GDNF expression and activity in inflammatory events associates with breast cancer.

Note:

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5 Role of the NADPH oxidase genes (nox) in TGF-beta signalling: Implications for hepatocarcinogenesis

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TGF-beta induces apoptosis in hepatocytes. This cytokine mediates reactive oxygen species (ROS) production that precedes the loss of mitochondrial-transmembrane potential, the release of cytochrome c and the activation of caspases. Looking for the origin of ROS, we have found that TGF-beta activates an NADPH oxidase-like system by a mechanism dependent on protein synthesis. Two genes of the NADPH oxidase family (nox): nox4 and nox1 are induced by TGF-beta in hepatocytes. The presence of NADPH oxidase inhibitors, such as DPI, blocks all the events related to the mitochondrial-dependent cell death process.

After injury, or loss of tissue, the liver regenerates, a process in which remaining cells start to proliferate to replace the tissue deficit. Regenerating hepatocytes are less sensitive than fetal or adult hepatocytes to the apoptotic response to TGF-beta. These cells show higher intracellular glutathione levels, which might provide mechanisms to avoid potential dangerous effects of the inflammatory process. In fact, treatment with BSO (a glutathione synthesis inhibitor) restores the response of regenerating hepatocytes to TGF-beta. Extracellular signals, involved in the regeneration process, might modify existing hepatocyte gene expression to meet new environmental demands. In this sense, EGF increases glutathione synthesis. Furthermore, we have recently found that EGF also impairs the TGF-beta-mediated nox4 induction. Resistance to TGF-beta would allow a faster recovery of the tissue mass during liver regeneration. However, during hepatocarcinogenesis, autocrine production of growth factors, such as TGF-alpha or HB-EGF, might increase cell antioxidant defenses, which would confer TGF-beta-resistance in terms of apoptosis. Furthermore, autocrine production of EGF receptor ligands might impair nox4 induction by TGF-beta. In this sense, recent results in FaO rat hepatoma cells indicate that this cytokine fails to induce nox4. Under these conditions, TGF-beta might contribute to tumour progression and metastasis, inducing epithelial-mesenchymal transition processes and contributing to tumor dissemination and metastasis.

6 Role of MMP-9 in B-chronic lymphocytic leukemia cell migration and invasion, and its regulation by alpha4beta1 integrin and CXCR4

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B-cell chronic lymphocytic leukemia (B-CLL), the most common leukemia in the Western world, consists in the accumulation of mature CD5 B cells in the peripheral blood and the progressive infiltration of lymphoid organs. We have studied the role of metalloproteinases (MMP) in B-CLL migration and tissue invasion, and their regulation by integrins and chemokine receptors. B-CLL cells from 12 different patients constitutively expressed MMP-9, but not MMP-2 or surface MT1-MMP. Expression of MMP-9 was significantly higher in B-CLL than in normal B cells. Adhesion of B-CLL cells to the fibronectin fragment FN-H89 or to VCAM-1, two known ligands for alpha4beta1 integrin, significantly enhanced MMP-9 gelatinolytic activity. This effect required PI3-K/Akt activity. The chemokine CXCL12 also increased MMP-9 activity in an ERK-dependent but PI3-K independent manner, indicating that alpha4beta1 and CXCL12 activated MMP-9 independently. Inhibition of MMP-9 by antibodies, inhibitors or RNA interference impaired B-CLL cell invasion through basement membranes and transendothelial migration. Adhesion of B-CLL cells, but not normal B cells, to FN-H89 or VCAM-1 also induced formation of podosomes, detected by actin, vinculin, and gelsolin staining. MMP-9 localized to these podosomes and this required PI3-K/Akt, but no other signaling. These results indicate an important physiological role for integrins and chemokine receptors in the regulation of MMP-9 in B-CLL and thus, in the migration and tissue invasion of these cells.

7 2-Methoxyestradiol, a superoxide dismutase inhibitor, induces VDAC-dependent apoptosis in chronic lymphocytic leukemia cells.

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Chronic lymphocytic leukemia (CLL) is characterized by the accumulation of long-lived B-lymphocytes. Most of the circulating cells appear to be non-dividing and the clonal excess of B cells is mainly caused by defects that prevent apoptosis. It has been reported that 2-methoxyestradiol (2-ME) inhibits superoxide dismutase (SOD) and induces apoptosis in leukemia cells through a ROS-mediated mechanism. We have investigated the mechanism of 2-ME-induced apoptosis in CLL cells. When freshly isolated CLL cells were incubated with 2-ME, a substantial accumulation of cellular superoxide measured by DHE was observed within 24 hours. Furthermore, N-acetyl-L-cysteine was able to decrease superoxide production and inhibit 2-ME-induced apoptosis measured by MTT. 2-ME-induced apoptosis was inhibited by Z-VAD.fmk, a caspase inhibitor. Dithiocyanatostilbene-2,2-disulfonic acid, an inhibitor of voltage-dependent anion channel (VDAC), decreased 2-ME-induced apoptosis, but not fludarabine-, dexamethasone-, or aspirin induced apoptosis. Ruthenium red inhibits calcium transport through membrane channels, and the combination of ruthenium red and 2-ME had a synergic effect in the induction of apoptosis in CLL cells. Finally, we found that 2-ME induced apoptosis in CLL cells, whereas T cells from these patients were not affected. Furthermore, when lymphocytes from healthy donors were incubated with 2-ME for 24 hours, viability was markedly reduced in B cells but not in T cells. Our results indicate that 2-methoxyestradiol induces superoxide production and VDAC-dependent apoptosis in chronic lymphocytic leukemia cells.

8 The role of Bile acids in NFKB mediated cancer progression in patients with the inflammatory condition Barrett's oesophagus

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Chronic reflux of stomach contents causes severe oesophagitis and a histological change in the lower oesophagus, from squamous mucosa to columnar mucosa. This metaplastic alteration is known as Barrett's oesophagus and predisposes sufferers to developing oesophageal adenocarcinoma (OA). The particular component of the refluxate responsible for this histological change and the carcinogenesis therein is unknown, but bile acids are suspected to play an important role.

We have been investigating the accumulation of molecular defects in the histological series leading from Barrett's oesophagus to OA, as well as investigating the molecular effects of bile acid exposure in vitro. A common finding from both the in vitro and in vivo studies has been the activation of the NFKB transcription factor. NFKB is activated throughout the histological series to OA (oesophagitis, Barrett's metaplasia, dysplasia and OA) (1,2) and is also activated by physiological doses of the secondary bile acid deoxycholic acid (3). We have recently shown that deoxycholic acid activates NFKB via a ROS-mediated mechanism. Deoxycholic acid stimulates the release of ROS within 60 minutes as measured by protein carbonyl group appearance and by measuring ROS directly with ROS-sensitive fluorescent dyes. The induction of ROS by bile acids is consistent with findings showing increased ROS levels in Barrett's patients and increased ROS induced DNA damage. The specific upstream events leading to NFKB activation by deoxycholic acid are currently under investigation.

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9 Interleukin-6 signaling is required for BRAFE600-induced senescence

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The RAS/RAF/MEK/ERK pathway represents a major mitogenic signaling pathway, and its constituents are often mutated in cancer. One of these mutants, BRAFE600, is often found in melanoma, and renders the RAS/RAF/MEK/ERK pathway constitutively active. However, introduction of this BRAF mutant does not immortalize primary cells, but instead induces senescence in vitro. Recently, we and others have provided evidence suggesting that oncogene-induced senescence plays an important role also in vivo. Specifically, whereas up to 80% of human nevi (moles) harbor BRAFE600-mutations, we found that nevi display characteristics of senescence, including elevated levels of the p16INK4A tumor suppressor gene and activation of a common senescence marker, SA- β -Galactosidase. These observations suggest that senescence restricts outgrowth of benign nevi to melanoma. Interestingly, we obtained evidence, both in vitro and in vivo, that in addition to p16INK4A, other factors must contribute to the maintenance of the senescent state of BRAFE600-expressing cells. We have begun to follow up on these observations, focusing on putative tumor suppressors that contribute to the BRAFE600-induced premature senescence response. In one of these approaches, we postulated that genes that are required for BRAFE600-induced senescence might be activated -similar to p16INK4A- by transcriptional upregulation during the senescence response. Therefore, we performed microarray analysis on BRAFE600-expressing, senescent human fibroblasts, relative to a number of control samples. We found that the interleukin IL-6 was specifically upregulated during BRAFE600-induced senescence. To determine any contribution of elevated levels of IL-6 to BRAFE600-induced senescence, we designed multiple shRNAs against IL-6 and found that knockdown of IL-6 abrogated the senescence response and led to continuous proliferation. Currently, we are determining whether the contribution of interleukins to BRAFE600-induced senescence is specific for IL-6 or reflects a more general phenomenon, and are in the process of identifying critical additional players in this pathway.

10 Inhibition of Heme Oxygenase-I Interferes with the Transforming Activity of the Kaposi's Sarcoma Herpesvirus-Encoded G protein-Coupled Receptor

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Heme oxygenase-I (HO-I), the inducible enzyme responsible for the rate-limiting step in the heme catabolism, is highly expressed in AIDS-Kaposi's sarcoma (KS) lesions and its expression is upregulated by the Kaposi's sarcoma-associated herpesvirus (KSHV) in endothelial cells. However, the mechanisms underlying KSHV-induced HO-I expression are still unknown. One of the key KSHV genes involved in KS development is the oncogenic G protein-coupled receptor (KSHV-GPCR or vGPCR). In this study we investigated whether vGPCR activated HO-I expression and if so, the putative role of HO-I in vGPCR-induced transformation. Here we show that vGPCR induces HO-I mRNA and protein levels in fibroblasts and endothelial cells. Targeted knock-down gene expression of HO-I by shRNA and chemical inhibition of HO-I enzymatic activity by Sn protoporphyrin IX (SnPP), impaired vGPCR-induced survival, proliferation, transformation, and VEGF-A expression. Moreover, vGPCR-expressing cells implanted in the dorsal flank of nude mice developed tumors with elevated HO-I expression and activity. Chronic administration of SnPP to the implanted mice, under conditions that effectively blocked HO-I activity and VEGF-A expression in the transplanted cells, strikingly reduced tumor growth, without apparent side effects. These data postulate HO-I as an important mediator of vGPCR-induced tumor growth and suggest that inhibition of intratumor HO-I activity by SnPP may be a potential therapeutic strategy.

II Skin Carcinogenesis in S100A9 null mice

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S100 proteins are a large family of low molecular weight calcium-binding proteins that have a tissue specific distribution. Dysregulation of S100 proteins has been associated with cancer, in particular the S100A4 null mice have an elevated number of spontaneous tumours (1) and decreased engraftment and metastasis of syngeneic cancer cells (2).

S100A9 and its heterodimeric binding protein, S100A8, are abundantly expressed in myeloid cells, constituting 40% of neutrophil cytosolic protein and 1% of monocyte cytosolic protein (3). S100A9 message has been detected in keratinocytes during the DMBA/TPA skin carcinogenesis model (4). To evaluate a potential role for this complex in cancer, a skin carcinogenesis study of the S100A9 null mice (5) (which also lack S100A8) was undertaken.

The S100A9 null mice showed no difference in the growth of injected syngeneic B16 and 3LL tumour cells compared to C57BL/6J controls. However, the S100A9 mice showed increased susceptibility in the DMBA/TPA skin carcinogenesis model, having increased papilloma multiplicity. Expression of the S100A9 protein was seen in C57BL/6J mice in the hyperproliferative epithelium restricted to papillomas, with the rest of the epithelium being negative. Expression was in a non-proliferative Ki67 negative population of cells.

As S100A8/9 can be expressed by both keratinocytes and neutrophils the absence of this protein may be exerting its effect through either cell-type. To begin to dissect the function of S100A8/9 in skin tumourigenesis, studies are underway to enumerate the neutrophil influx and level of inflammation in C57BL/6J and S100A9 null skin in this model.

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12 Analysis of genetic and epigenetic alterations in a chronic inflammation model of lung cancer induced by silica

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Single silica intratracheal instillation in rat induces a multistep lung carcinogenic process mediated by a chronic inflammatory process with sequential appearance of preneoplastic lesions and peripheral lung epithelial tumors. To gain insight into the molecular mechanisms that could lead to inflammation-related carcinogenesis we have studied genetic and epigenetic alterations throughout the multistep process. Promoter hypermethylation of lung cancer related tumor suppressor genes (TSG's) was analyzed in the resected tumors. E-cadherin (67%), H-cadherin (78%), APC (56%) and p16 (89%) showed strong promoter hypermethylation. Strong correlation was also observed between p16 promoter hypermethylation and loss of p16 protein. The status of p53, hTERT and p16 protein was also studied by immunohistochemistry. p53 protein was frequently accumulated in tumors as compared to normal and hyperplastic bronchioloalveolar areas. Nuclear p16 protein and hTERT were significantly accumulated in hyperplastic bronchiolar epithelium and their expression was significantly decreased in tumors. We have also investigated the epigenetic and genetic alterations of the Ras family of genes, and the mutational status of EGF-R and p53 by genomic sequencing of relevant exons after laser microdissection. We did not find mutations in either K-ras, N-ras, c-H-ras and EGF-R, and only 3 cases were detected with mutations for p53 (3/22). We did not observe promoter hypermethylation of Rassf1A and Nore1A. Taken together, these data show that "classical" mutations found in human lung cancer are not generally involved in silica-induced rat lung carcinogenesis. However, promoter hypermethylation in relevant TSG's and key protein alterations in the p53/p16/hTERT pathways seem to play a role in the progression of these tumors. In conclusion, the silica-induced lung carcinogenesis model recapitulates many of the histopathological features observed in human lung peripheral tumors and represents a good tool to study the molecular events involved in the multistep lung carcinogenesis process in the context of chronic inflammation.

13 Modulation of p53 function by IKK

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Hypoxia is involved in a number of physiological and pathological processes. In addition to stimulating pro-angiogenic signals, hypoxia can also induce apoptosis. At least in part, this is mediated by the tumour suppressor p53, a crucial determinant of the cellular response to stress. Following genotoxic damage, p53 activates genes involved in DNA repair, cell-cycle arrest and apoptosis. Less is known about p53 activation by hypoxia. Here we have investigated p53 function following treatment with the hypoxia mimetic drug Deferoxamine (DFX). We have found that DFX induces p53 activation, leading to upregulation of pro-apoptotic target genes such as puma, bax, and noxa. Surprisingly, p53 activity and stabilisation was dependent on I κ B kinase (IKK β). IKK β is best known as a regulator of the NF- κ B pathway, through phosphorylation of I κ B α and the RelA NF- κ B subunit. Due to the role of NF- κ B in tumourigenesis, IKK has been identified as a target for the development of new cancer treatments. Using siRNA and chemical inhibitors of IKK β , we found that p53 function was inhibited following DFX treatment. These effects were also observed using IKK β null mouse embryonic fibroblasts. Furthermore, IKK β modulation of p53 was specifically seen following DFX treatment and not with other typical p53 activating stimuli such as UV.

These results define a novel pathway for p53 activation and a new function for IKK β . Moreover, they suggest that the use of IKK inhibitors in cancer types that still possess a functional p53 could be detrimental to a positive treatment outcome.

14 Tumor microenvironment and mitotic checkpoint are key factors in the outcome of classical Hodgkin Lymphoma

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Hodgkin Lymphoma (HL) is a lymphoid neoplasia in which the malignant cells represent a minor population within the affected tissue, which mainly consists of a inflammatory infiltrate of nontransformed cells (T- and B-lymphocytes, macrophages, eosinophils, fibroblasts). The malignant cells derive from B-cells that lack a functional B-cell-receptor, a situation that should lead to apoptosis. However, a complex network of cytokine- and adhesion-molecule-mediated interactions among the neoplastic and the inflammatory cells is thought to promote the proliferation and survival of the malignant cells. Around 20-30% of HL patients do not respond to chemotherapy and finally succumb to their disease, and the factors that influence the treatment response and outcome of HL are essentially unknown.

We analyzed the gene-expression profiles of samples from 29 HL patients and compared the profiles of patients with favourable and unfavourable treatment response. We identified 145 genes associated with clinical outcome, which were grouped into gene-expression “signatures” expressed by either the neoplastic cells or the inflammatory cells. Upregulation of genes expressed by T-cells (CD8B1, CD3D, SH2D1A) and macrophages (ALDH1A1, lysozyme, STAT1), implying a predominant cytotoxic T-cell response and the presence of tumour-associated macrophages, was associated with unfavourable treatment response. Conversely, expression of genes involved in extracellular matrix remodeling, fibroblast function, chemotaxis and antigen presentation (TIMP4, LAMB1, CCL26, HLA-DRB3) was associated with favourable outcome. On the other hand, a cell-cycle signature mainly expressed by the malignant cells was also related to poor clinical outcome, implying that the features of both the neoplastic and inflammatory cells determine treatment response. We performed immunohistochemical staining in an independent series of 235 patients, confirming the association between the expression of eight genes (expressed by either T-cells, macrophages, or malignant cells) and disease outcome.

These results suggest that the clinical behaviour of HL is a result of the interaction between the neoplastic cells and their inflammatory microenvironment. Additionally, we have identified potential novel prognostic markers and therapeutic targets for the treatment of HL.

15 Role of PKC-beta enzymatic function in regulating cell survival mediated by B cell antigen receptor cross-linking

Chandrasekar Venkataraman, Xinyi Cynthia Chen, Songqing Na, Linda Lee, Kuldeep Neote, and **Seng-Lai Tan**
Cancer Inflammation and Cell Survival, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Indiana, USA

Cross-linking of the B cell antigen receptor (BCR) results in the activation of several protein tyrosine kinases leading to phospholipase C-gamma2-dependent phospholipid hydrolysis and Ca² mobilization, followed by activation of the protein kinase C (PKC) family members. Sustained Ca² release in B lymphocytes is dependent on the membrane localization and activation of the protein tyrosine kinase BTK. Ca² release is a tightly regulated process involving BTK membrane localization through its phosphorylation by PKC-beta. A selective role of PKC-beta in B cell signaling was first revealed by the characterization of PKC-beta knockout mice, which displayed decreased B cell proliferation in response to various mitogenic stimuli. However, it is not clear whether the B cell defects displayed by the PKC-beta knockout mice are due a B cell developmental defect or the scaffolding function of PKC-beta, resulting in a defect in the recruitment or formation of signal transducing complex molecules. Thus, in this report we investigated the effects of pharmacologic inhibition of the catalytic function of PKC-beta on B cell survival and growth. Treatment of Daudi B lymphoma cell line with a selective PKC-beta inhibitor, LY333531, inhibited anti-IgM-induced phosphorylation of BTK on Ser180 in a concentration-dependent manner, which was concomitant with an increase in BTK activation, and Ca² mobilization. In primary splenic B cells, LY333531 inhibited BCR-induced B cell proliferation, but did not affect basal or LPS-induced proliferation. Finally, LY333531 treatment resulted in the induction of apoptosis of anti-IgM-activated B cells, which corroborated with their inability to up-regulate pro-survival factors, Bcl-XL and Bcl-2. These results support the important and selective role of the PKC-beta enzymatic function in controlling Ca² release during BCR signaling leading to B lymphocyte survival and growth.

16 Generation of human melanoma cell lines with stable interference or overexpression of CXCR4 and MTI-MMP for in vivo metastasis studies.

Rubén A. Bartolomé, Maria E. Miquilena, Lorena Martínez-Prats, Sergio Ferreiro, Rafael Delgado and **Joaquín Teixidó**

Centro de Investigaciones Biológicas, CSIC, Madrid, Spain.

Servicio de Microbiología, Hospital 12 de Octubre, Madrid, Spain.

Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid, Spain.

Increasing experimental and clinical data indicate that chemokines and their receptor might contribute to tumour cell metastasis (1,2). Melanoma cells express CXCR4, the receptor for chemokine CXCL12, which confers them with migratory and invasive capacity (3,4). We previously reported that CXCL12 induces melanoma cell invasion across basement membranes involving stimulation of the metalloproteinase MTI-MMP (5,6). We have generated by retroviral gene transfer several sublines from the highly metastatic melanoma cell line BLM, with stable overexpression or interference of CXCR4 or MTI-MMP expression. CXCR4 and MTI-MMP expression in these sublines has been assessed by Western blotting and flow cytometry. Furthermore, these sublines have been functionally characterized in 2D-migration and 3D-invasion assays, confirming the important role of both proteins in the invasion process. Also, activation of MMP-2 was inhibited in the sublines with interfered MTI-MMP expression. The BLM sublines have been injected in SCID nude mice to assess their in vivo metastatic properties. The results from this work will contribute to elucidate the role of CXCR4 and MTI-MMP during metastasis of melanoma cells.

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Organisers and Invited Speakers' Portfolio

A compilation of short scientific biographies of organisers and speakers in accordance with the order of the programme



Raymond N. DuBois, M.D., Ph.D.

B.F. Byrd Jr. Professor of Oncology
Professor of Medicine and Cancer Biology
Director, Vanderbilt-Ingram Cancer Center
Nashville, TN, USA

Raymond N. DuBois is currently the B.F. Byrd Professor of Molecular Oncology, Professor of Medicine, Cancer Biology, and Cell/Developmental Biology and Director of the Vanderbilt-Ingram Cancer Center. His research is focused on developing novel approaches for the early detection, prevention and treatment of colorectal cancer.

Specifically, he has focused on targeting the COX-2 pathway, which is involved in the promotion of preneoplastic colorectal lesions. His group has detailed the molecular effects of increased prostaglandin production in cancer and its biomarkers as well as downstream and heterologous signaling pathways

modified by them. He leads a successful NCI-funded Program Project focused in prostaglandin biology at Vanderbilt. His work was a major basis for the use of COX-2 inhibitors in colorectal prevention trials and for which he received the 2004 AACR Landon Prize for Translational Research. He also received the AGA Distinguished Achievement Award and was elected as a Fellow in the American Association for the Advancement of Science for his outstanding contributions toward scientific advancement in the field of cancer research and this year he was selected to receive the Anthony Dipple Carcinogenesis Award by Oxford University Press.

DuBois currently serves on the Board of Scientific Advisors to the Director of the National Cancer Institute. He is also a member of the Board of Directors for the American Association for Cancer Research and Chairman of the Board of Directors for the Keystone Symposia on Molecular and Cellular Biology. He was selected as a member of the Scientific Advisory Board for the National Colorectal Cancer Research Alliance. He is a well known cancer researcher who has numerous scholarly publications, editorial duties and research grants.



Yinon Ben-Neria, M.D., Ph.D.

The Lautenberg Center for Immunology
Hebrew-University-Hadassah Medical School
Jerusalem, Israel

The scientific studies and career of Yinon Ben-Neria are summarised below:

M.D.-Ph.D. at Tel Aviv University and the Weizmann Institute.

Postdoctorate with David Baltimore at the Whitehead Institute: molecular cloning of cAbl and Mdr1 and characterizing the p210^{bcr-abl} protein.

1986- present: a faculty member of the Hebrew University Medical School.

His research accomplishments are: identifying and cloning the ER-redox-dependent protein tyrosine kinase LTK; elucidating the essential role of I κ B degradation in NF- κ B activation (with P. Baeuerle); role of inducible I κ B phosphorylation, ubiquitination; identification of the

I κ B degradation motif (with A. Ciechanover) and b-TrCP as the I κ B-E3; the b-catenin phosphorylation complex at the Wnt pathway and the trigger of b-catenin phosphorylation-ubiquitination; the role of NF- κ B in liver innate immunity and cancer.



Jorge Moscat, Ph.D.

Research Professor

Centro de Biología Molecular “Severo Ochoa”, CSIC-UAM
Madrid, Spain

Jorge Moscat did his Ph.D. Thesis under the supervision of Amador Schüller and Angel Martín Municio at the Hospital San Carlos, Madrid. His research focused on signal transduction mechanisms in hepatocytes. He obtained his Ph.D in Biochemistry and Molecular Biology in 1984 from the Universidad Complutense, Madrid.

Moscat then worked on platelet activation and arteriosclerosis at the Hospital Gregorio Marañón, Madrid.

During his stays in 1987 and 1988 to the NCI (Bethesda, USA), Moscat got interested in the study of the signalling mechanisms that regulate growth and differentiation that are altered in tumoral processes.

In 1990, Moscat joined the Center of Molecular Biology “Severo

Ochoa” where he has remained until recently. This year, 2006, Moscat took a position as Professor at the University of Cincinnati (USA).

His research is focused on the identification of kinases and modulators involved in inflammatory processes and tumorigenesis. His laboratory has characterised new therapeutic targets for these diseases with the goal of identifying more effective and selective drugs. He holds seven patents and several contracts with industries.

Moscat has received the following prizes: Real Academia de Ciencias (1999), Fundación Carmen and Severo Ochoa (2000), and the special Grant for Basic Research from the Fundación Juan March.



Neil D. Perkins, Ph.D.

Principal Investigator
School of Life Sciences, University of Dundee
Dundee, Scotland, UK

The studies and scientific career of Neil Perkins can be summarised as follows:

Undergraduate degree, University of Sheffield, UK (1983-1986)

Ph.D., Chester Laboratories, Institute of Cancer Research, University of London, UK (1986-1990)

Postoc, Howard Hughes Medical Institute, University of Michigan Medical Center, Ann Arbor, USA (1990-1996)

Principal Investigator, Division of Gene Regulation and Expression, School of Life Sciences, University of Dundee, Scotland UK (1996 - present).

His laboratory is interested in how NF-kappaB subunits are regulated by oncogenes, tumour suppressors and

stimuli associated with cancer development and therapy. In particular, they have found that the ARF and p53 tumour suppressors as well as certain inducers of NF-kappaB DNA-binding activity, such as ultraviolet light and some chemotherapeutic compounds, can induce the association of NF-kappaB subunits with transcriptional corepressor complexes, allowing them to function as repressors rather than activators of gene expression. The identification of these pathways suggests that NF-kappaB can function as a tumour suppressor as well as a tumour promoter. His laboratory is investigating the mechanisms regulating these pathways and also the implications of these results for both traditional and NF-kappaB based cancer therapy.



Michael Karin, Ph.D.

Distinguished Professor of Pharmacology
University of California at San Diego
San Diego, CA, USA

Michael Karin was born in Tel Aviv, Israel and received the Bachelor of Science degree in 1975 from Tel Aviv University, with a major in Biology. In 1975 he arrived in the US and in 1979 received a Ph.D. degree in Molecular Biology from the University of California, Los Angeles. Karin followed his graduate studies with postdoctoral fellowships at the Fox Chase Institute for Cancer Research, working in the laboratory of Beatrice Mintz, and the laboratory of John Baxter at the University of California, San Francisco. He then joined the faculty at the University of California, San Diego in 1986, where currently he is a Distinguished Professor of Pharmacology.

Michael Karin has received numerous awards including the Oppenheimer Award for Excellence in Research from the Endocrine Society, The Herman Beerman Lectureship from the Society of Investigative Dermatology, C.E.R.I.E.S.,

Research Award for Physiology or Biology of the Skin, The Grossman Lectureship from the American Gastroenterology Association and an American Cancer Society Research Professorship in 1999. Karin was elected to the National Academy of Sciences in 2005. Karin also serves on several advisory boards and was cofounder of Signal Pharmaceutical (currently Celgene).

Karin's research interests focus on five areas of study. 1) Regulation of transcription in mammalian cells by steroid hormones, growth factors, adverse environmental conditions and during cellular differentiation. The Karin lab has used a variety of biochemical and genetic approaches to isolate transacting regulatory proteins, which mediate responses to developmental, hormonal and environmental signals. Current efforts are to understand the regulation of gene transcription by growth factors, cytokines and microbial pathogens. 2) Response of the mammalian genome to stress. The molecular basis for the UV response, the mammalian counterpart of the bacterial SOS response, is being studied by various molecular genetic and biochemical techniques. 3) Protein kinase cascades and their role in growth control, cell differentiation and programmed cell death. These studies focus

on the JNK and p38 MAP kinase cascades and their roles in cellular regulation and specific gene induction. 4) The IKK/NF- κ B signaling pathway and its physiological and pathophysiological functions. In addition to the biochemical identification of IKK and elucidation of the NF- κ B activation pathway, the Karin Lab has been a major driving force in studying IKK and NF- κ B as important links between chronic inflammation and cancer. These studies utilize biochemical as well as whole animal approaches. 5) The regulation of mRNA turnover. In addition to gene transcription, an important control point that determines gene expression levels, is mRNA turnover. The Karin lab had elucidated the major mechanism that contributes to rapid mRNA decay in mammalian cells and identified several RNA binding proteins that modulate this process. These proteins serve as targets for phosphorylation cascades that lead to stabilization of specific mRNAs in response to environmental stimuli.

Michael lives in La Jolla with his wife and three sons. While not being occupied with research and advisory activities he enjoys scuba diving, kayaking and camping in Baja California and the Anza Borrego desert.



Sankar Ghosh, Ph.D.

Professor
Section of Immunobiology, Department of Molecular
Biophysics and Biochemistry
Yale University School of Medicine
New Haven, CT, USA

Sankar Ghosh's scientific career can be summarised as follows: 1989-91; Postdoctoral Fellow with David Baltimore, Whitehead Institute for Biomedical Research, Cambridge, MA

1991-1997; Assistant Professor, Section of Immunobiology and Department of Molecular Biophysics and Biochemistry, Yale University School of Medicine

1997-2000; Associate Professor, Section of Immunobiology, Department of Molecular Biophysics and Biochemistry, Yale University School of Medicine

2000-present; Professor, Section of Immunobiology, Department of Molecular Biophysics and Biochemistry, Yale University School of Medicine

His laboratory wishes to understand the mechanisms that operate in the signal transduction pathways that lead to NF- κ B activation, as well as the regulatory mechanisms that control the activity of NF- κ B in the nucleus.

Sankar Ghosh has received numerous Honors and Awards, such as:

Sir R.B. Ghosh Fellowship of Calcutta University for Study abroad (1981)

Irvington Institute for Medical Research Postdoctoral Fellowship (1989)

MERIT Award, NIH (2001)

American Association of Immunologists-Pharmingen Investigator Award (2002)

Member, Faculty of 1000, 2002-present



Ann Richmond, Ph.D.

Ingram Professor and Vice Chair
 Department of Cancer Biology
 Assistant Dean of Biomedical Research, Education and Training
 Associate Director of Education, Vanderbilt Ingram Cancer Center
 Vanderbilt University School of Medicine
 Senior Career Scientist
 Department of Veterans Affairs
 Nashville, TN, USA

Ann Richmond is a Professor in the Department of Cancer Biology at Vanderbilt University School of Medicine. Her research interests include transcriptional regulation of chemokines, the role of chemokines in chronic inflammatory conditions, wound healing and tumor progression, as well as signal transduction mechanisms involved in chemokine mediated chemotaxis. Her laboratory has extensively studied the factors contributing to the constitutive transcription of angiogenic chemokines during tumor progression. They are currently testing the utility of targeting the transcription factor, NF- κ B, as a therapeutic approach for treatment of malignant melanoma. Work from her lab has also elucidated the role

of ligand mediated receptor phosphorylation in the facilitation of chemokine receptor desensitization. Moreover, her research team has shown that ligand mediated receptor internalization is associated with cessation of burst of chemokine signaling mediated through the chemokine receptor, CXCR2, which is required for continuous response to a chemokine. Mutation of the receptor such that ligand no longer mediates internalization of the receptor is accompanied by prolonged response to ligand with regard to generation of IP₃, calcium mobilization, and other intracellular signals. However, loss of receptor internalization is accompanied by a loss of the chemotactic response, even through there is an increased length and strength of intracellular signals. Data to date suggest that it is the oscillation of signals that is required for a chemotactic response.

Moreover, the activation signals need to localize at the leading edge or the uropod of the migrating cell. Using state of the art microfluid devices, time lapse video microscopy, FRET analysis of localized activation of Rac-1, Cdc42 and Rho GTPases, Richmond's research group is characterizing the mechanism by which altered adaptor binding to chemokine receptors or altered internalization of receptors alters the chemotactic response. Ongoing research is aimed at examination of the mechanism by which receptor internalization facilitates the establishment of an intracellular gradient of signals to establish polarity oscillations required for response to a chemotactic gradient with the end result leading to a better understanding of how chemokines mediate cancer cell metastasis as well as chronic inflammatory conditions.

■ 2006 CNIO Cancer Conference: Inflammation and Cancer
Session II: Crosstalks in Inflammation and carcinogenesis



Timothy R. Billiar, M.D.

Chair of the Surgery Department and
George V. Foster Professor of Surgery
University of Pittsburgh, Pittsburgh, USA

Timothy R. Billiar received his MD degree from the University of Chicago in 1983. This was followed by surgical training at the University of Minnesota and the University of Pittsburgh from 1983 – 1992, which included a four-year research fellowship. In 1992 he joined the faculty of the Department of Surgery at the University of Pittsburgh as a Samuel P. Harbison Assistant Professor of Surgery. In 1999, he was named Chair of the Surgery Department and George V. Foster Professor of Surgery at the University of Pittsburgh.

Timothy Billiar's long-standing interest has been in mechanisms of inflammation-induced organ dysfunction and injury. This interest led his laboratory to first describe the

expression of the inducible nitric oxide synthase in non-macrophage cell types. His laboratory was also the first to identify inducible nitric oxide synthesis in humans and the first clone to characterize the human inducible NO synthase in 1993. More recent work has characterized the pro- and anti- apoptotic actions of nitric oxide as well as inflammatory signaling pathways within liver cells. This has led to a greater understanding of inflammatory signaling following acute injury and infection.

Timothy Billiar has served in leadership positions in a number of national and international societies. He is past president of the Society of University Surgeons and current president of the International Nitric

Oxide Society and the Surgical Infection Society. His laboratory has been funded by the National Institutes of Health since 1989 and he has served as a member of NIH Study Sections. Billiar is on numerous Scientific Advisory Boards. He has served on the Editorial Board of ten journals and is a member of the American Society for Clinical Investigation.



Santos Mañes, Ph.D.

Department of Immunology and Oncology
Centro Nacional de Biotecnología /CSIC
Madrid, Spain

Santos Mañes obtained his PhD in Biochemistry and Molecular Biology at the Universidad Autónoma de Madrid in 1999, under the direction of Carlos Martínez Alonso. He was then appointed group leader at the Department of Immunology and Oncology, a department co-funded by Pharmacia (now Pfizer) and the Spanish National Research Council, at the National Center for Biotechnology (CNB). At that time, S. Mañes conducted research on the physiopathology of chemokine receptors, focusing on three main aspects: (a) the spatio-temporal regulation of chemokine-induced leukocyte and tumor cell chemotaxis, (b) the cell biology of human immunodeficiency virus (HIV) infection, and (c) the function of chemo-

kines in tumor-stroma communication. His laboratory made seminal observations on the requirement for chemokine receptor association to membrane microdomains (termed lipid rafts) to function as chemotactic receptors in leukocytes and malignant cells. His group demonstrated that association of chemokine receptors to membrane rafts is not only a key event in organizing polarized signaling in migrating cells, but also for their function as coreceptors for HIV-1 infection. In 2001, he described the interaction between chemokines and growth factors in the tumor environment, and the relevance of this crosstalk in regulating tumor cell invasion.

Mañes was tenured in 2004 at the Spanish National Research

Council (CSIC). His research currently focuses on understanding how different chemokine/chemokine receptor pairs regulate the immune response to tumors.

Selected publications:

Mañes et al. (2003). *Nat. Rev. Immunol* 3:557-68

Mañes et al. (2003). *J. Exp. Med.* 198:1381-9

Molon et al. (2005). *Nat. Immunol* 6:465-71



Lisa M. Coussens, Ph.D.

Associate Professor
Department of Pathology, Cancer Research Institute and
Comprehensive Cancer Center
University of California, San Francisco
San Francisco, CA, USA

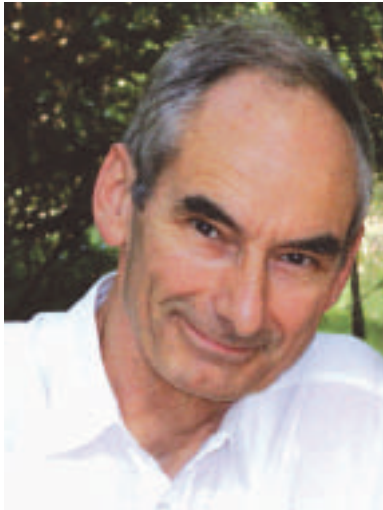
Lisa Coussens received her Ph.D. in Biological Chemistry from UCLA in 1993, and completed her post doctoral fellowship in Cancer Biology at University of California, San Francisco.

Lisa M. Coussens is an Associate Professor in Residence at the Cancer Research Institute and Pathology Department at the University of California, San Francisco. She is also a member of the UCSF Comprehensive Cancer Center, the UCSF Biomedical Sciences Program (BMS) and the Herbert Boyer Program in Biological Sciences (PIBS).

The overall goal of her laboratory's research is to define the cellular and molecular determinants of the step-wise pathways mediating epithelial carcinogenesis. Her research is

based upon the premise that, in addition to intrinsic changes occurring within neoplastic cells, e.g., activation of oncogenes and inactivation of tumor suppressor genes, extrinsic factors, e.g., extracellular matrix remodeling, inflammation, angiogenesis, and immune-surveillance, also regulate critical properties of tumor evolution. Her research team is currently investigating the role of diverse inflammatory cells, complement activation, extracellular proteases (serine, cystein, metallo), and extracellular matrix components, as regulators of cell proliferation, genomic instability, inflammation, angiogenesis, and malignant potential. The long term goal of this work is to translate these basic observations, made in the mouse, toward the

rational design of novel therapeutics whose aim will be to block and/or alter rate-limiting events critical for solid tumor growth in humans.



Hans Schreiber, M.D., Ph.D.

Professor

The University of Chicago, Department of Pathology,
Committee on Immunology, Committee on Cancer Biology,
and The Cancer Center,
Chicago, USA

The scientific studies and career of Hans Schreiber are summarised below:

1966-1969 Predoctoral work at the Institutes of Pathology and Radiation Biology at the University of Freiburg

1970-1973 Research Staff Member, Oak Ridge National Laboratory, Chemical carcinogenesis, Radiation biology

1973-1974 Medical Internship, Moabit University Hospital, Berlin, Germany

1974-1977 Fellow in Immunology of the National Cancer Institute in the Department of Pathology, University of Chicago

1977-1981 Assistant Professor of Pathology, University of Chicago and Member, Committee on Immunology

1982-1985 Associate Professor of Pathology, University of Chicago and Member, Committee on Immunology

1983-1984 Visiting Professor, Depart-

ment of Genetics, University of California, Berkeley

1986-Present Professor of Pathology, University of Chicago

2002-2003 Chairman, Committee on Immunology, University of Chicago

Immunology and genetics provide the most powerful tools to search for cancer-specific changes in malignant cells. Activation of known oncogenes appears to be only a small fraction of the many changes required for the development of malignancy, and a cell must escape other yet unknown host control mechanisms in order to become a cancer cell. Tumor-specific mutant proteins even when intranuclear can be recognized as peptides by T cells on the surface of tumor cells. Identification of the molecular and genetic basis of these antigens may identify critical causative mechanisms leading to cancer. These antigens may also represent powerful targets for selective immunological destruction of cancer cells without killing normal cells since the changes are cancer-specific. Genetic manipulations of the cancer or of the surrounding host tissue ("gene therapy") can make certain

cancer cells more immunogenic and/or reverse malignant growth. Some of the ongoing projects in Schreiber's laboratory are:

1. Identification of the genetic origins, molecular biology and function of tumor-specific antigens.
2. Development of novel approaches to inducing cancer-specific immunity against long-term established cancers. Approaches of using tumor stroma and tumor vessels as therapeutic targets.
3. Mechanism of escape of established cancers from host immunity. Special emphasis is placed on the role of tumor stroma, immunodominance and mechanisms of paracrine stimulation of tumor growth.
4. Mechanism of long-lasting growth arrest of cancer in the absence of T cells by certain cytokines, tumor necrosis factor and interferon gamma in particular.
5. Development of approaches to immune prevention of cancer development in genetically cancer-prone individuals using transgenic and chemical carcinogenesis models.



Michael J. Thun, M.D., M.S.

Vice President of Epidemiology and Surveillance Research
American Cancer Society
Atlanta, Georgia, USA

Michael J. Thun received a B.A. degree from Harvard College, an M.D. from the University of Pennsylvania School of Medicine, and a Master of Science in Epidemiology from the Harvard School of Public Health. He has worked for twenty-eight years in epidemiology and disease prevention, first as a Medical Officer investigating toxic exposures at the New Jersey State Health Department, and then as an Epidemic Intelligence Service Officer and staff scientist for the Centers for Disease Control and Prevention at the National Institute for Occupational Safety and Health (1980-1988). In 1989, Thun became Director of Analytic Epidemiology for the American Cancer Society (ACS) in Atlanta. Since 1998 he has served as

Vice President of Epidemiology and Surveillance Research, overseeing both cancer surveillance and studies on the causes and prevention of cancer. His research covers a wide range of issues within cancer epidemiology, including studies on the potential of aspirin as an anti-cancer agent, alcohol, obesity, the effects of active smoking and environmental tobacco smoke, and genetic and environmental risk factors for cancers. He is the author of approximately 300 publications, book chapters, books, and published proceedings. Michael J. Thun has served on many advisory groups including the Institute of Medicine and the Board of Scientific Counselors for the National Cancer Institute. He is an adjunct professor at the Emory

University, Rollins School of Public Health and Winship Cancer Center.



Martin J. Blaser, M.D.

Frederick H. King Professor of Internal Medicine
Chair, Department of Medicine
Professor of Microbiology
New York University School of Medicine,
Department of Medicine
New York, USA

Martin J. Blaser is the Frederick H. King Professor and Chair of the Department of Medicine and as Professor of Microbiology at New York University School of Medicine. He is currently President of the Infectious Diseases Society of America. Martin Blaser is interested in understanding the relationships between persistently colonizing bacteria and their multicellular hosts. His work has largely focused on *Helicobacter pylori* and *Campylobacter* species, which are important as pathogens and as model systems. His recent approaches have dealt with genetic and mathematical analyses of population diversity and structure. Recent work also has focused on microbial signaling of host cells, and long-term equilibrium

relationships, which are relevant to neoplasia. Another group of investigations is aimed at understanding the nature of the indigenous microbiota and their interactions with host tissues.



Zena Werb, Ph.D.

Professor and Vice-Chair
Department of Anatomy,
University of California
San Francisco, CA, USA

Zena Werb received her B.Sc. in Biochemistry from the University of Toronto. She received her Ph.D. in Cell Biology from Rockefeller University, working with Zanvil Cohn on macrophages. Her postdoctoral fellowship at Strangeways Research Laboratory in Cambridge England introduced her to proteases. She then joined the faculty of University of California when currently she is currently Professor and Vice-chair of the Department of Anatomy.

Werb is recognized internationally for her original and fundamental discoveries about the molecular and cellular basis of extracellular matrix proteolysis and its role in the normal functioning and pathogenesis of tissues. Her studies have fostered new paradigms about the role of the

cellular microenvironment and intercellular communication in development and cancer. She pioneered the concept that extracellular proteolysis is a mechanism of altering extracellular signaling. By using genetic, biochemical and cell biologic approaches Werb defined the critical role of MMPs in embryonic implantation, mammary and bone development, angiogenesis, stem cell biology and in neoplastic progression. Werb has published more than 330 papers.

Zena Werb has received many honors and awards including a John Simon Guggenheim Foundation Fellowship, FASEB Excellence in Science Award, and the Charlotte Friend Award of the American Association for Cancer Research. She has an honorary degree of Doctor

in Medicine from the University of Copenhagen. Dr. Werb is a member of the Institute of Medicine of the National Academy of Sciences and a fellow of the American Academy of Arts and Sciences. She has been an elected officer of the American Society for Cell Biology, the American Association for Cancer Research, the American Society for Matrix Biology and AAAS. She was the President of the American Society of Cell Biology in 2005. She is on the editorial boards of *Cell*, *Cancer Cell* and *Genes and Development*.



Albena T. Dinkova-Kostova, Ph.D.

Department of Medicine Division of Clinical Pharmacology
Johns Hopkins University School of Medicine
Baltimore, MD, USA

Albena T. Dinkova-Kostova received her B.A. and M.S. degrees in Biochemistry and Microbiology from Sofia University, Bulgaria and her Ph.D. in Biochemistry from Washington State University, USA. She was a postdoctoral fellow and a Research Associate at the Department of Pharmacology and Molecular Sciences at the Johns Hopkins Medical School and is currently is an Assistant Professor in the Division of Clinical Pharmacology, Department of Medicine. She works in the area of cancer prevention, is an author of 25 scientific papers, and a member of the editorial advisory boards of *Medicinal Chemistry* and *Minireviews in Medicinal Chemistry*.



Xin Wei Wang, Ph.D.

Senior Investigator
Head, Liver Carcinogenesis Section
Laboratory of Human Carcinogenesis
Center for Cancer Research
National Cancer Institute, NIH
Bethesda, MD, USA

Xin Wei Wang is a trained cancer biologist with a special interest in the molecular biology and genetics of human liver cancer. He holds a Bachelor's degree from Shanghai Medical University (1982), a Master's degree from the Chinese Academia of Science (1985) and a Ph.D. degree from New York University (1991). He completed postdoctoral fellowships at the Roche Institute of Molecular Biology (1991-1992) and at NCI (1992-1995) with studies on molecular carcinogenesis and signal transduction. He then served as a Senior Staff Fellow at NCI (1995-1998). He was recruited as a tenure-track investigator in the Laboratory of Human Carcinogenesis, NCI in 1998, and received tenure as a Senior Investigator in

2005. Currently, he serves as the Head of the Liver Carcinogenesis Section in Laboratory of Human Carcinogenesis, NCI, and as an Adjunct Associate Professor at the University Of Maryland School Of Medicine. His research group has been focusing on human hepatocellular carcinoma to dissect genetic and biochemical pathways important in this disease. Two areas of study include defining the role of Crml/Ran complex in early stages of hepatocarcinogenesis (Forgues et al, Mol Cell Biol 2003; Wang et al, Nat Cell Biol 2005) and determining the molecular portraits of primary and metastatic liver cancer by gene expression profiling and supervised machine learning (Ye et al, Nat Med 2003; Kim et al, Hepatology 2004).

He has published over 76 manuscripts and book chapters, and has been frequently invited to give lectures both nationally and internationally. In addition, he provides numerous editorial services and grant reviews.



Manuel Serrano, Ph.D.

Head, Tumor Suppressor Group
Molecular Oncology Program
CNIO
Madrid, Spain

Manuel Serrano began his scientific career at the Center of Molecular Biology “Severo Ochoa” (Madrid), in the laboratory of Margarita Salas. In 1992, he joined the laboratory of David Beach, in Cold Spring Harbor Laboratory (New York) as a Postdoctoral Fellow. During this time, Serrano discovered a new cell cycle regulator, p16, one of the most important tumor suppressor genes. Since then, his scientific activity has mainly focused on investigating the mechanisms of tumor suppression. In 1997, he returned to Spain to initiate an independent research group at the National Center of Biotechnology - CSIC in Madrid. Together with his research group, Serrano moved to the CNIO in 2003. The “Tumor

Suppression Group” directed by Serrano at the CNIO has made outstanding discoveries in recent years. Among their main contributions are: the characterization of the tumor suppressors p16 and Arf as sensors of oncogenic stress and the mechanisms that regulate their expression; the description and identification of oncogenically-stressed, senescent, cells in tumors; and, the generation of genetically modified mice that are resistant to cancer.



Masayuki Yamamoto, M.D., Ph.D.

Professor, Center for Tsukuba Advanced Research Alliance and Graduate School of Comprehensive Human Sciences, University of Tsukuba, and Project Director, Environmental Response Project, Exploratory Research for Advanced Technology, Japan Science and Technology Corporation University of Tsukuba, Tsukuba, Japan

Masayuki Yamamoto was graduated from Tohoku University School of Medicine in 1979 and from Tohoku University Graduate School of Medicine in 1983. His advisor was Goro Kikuchi. He obtained a Doctor of Medical Sciences degree (PhD) in 1983 for his study on the metabolic regulation of heme biosynthesis. In 1983-1986, Yamamoto was a postdoctoral fellow at Northwestern University with James Douglas Engel. During this period, he cloned erythroid-type 5-aminolevulinate synthase (ALAS-E) cDNA, and conclusively proved the presence of erythroid isozymes in heme biosynthetic enzymes.

In 1989, Yamamoto visited the Engel laboratory again and in collaboration identified the GATA

family of transcription factors, which are now widely studied and one of the prototype transcription factor families regulating lineage commitment and cell differentiation. In 1991, Yamamoto returned to Japan and started the analyses on the regulation of *Gata1* and *Gata2* genes during hematopoiesis. He clarified the unique structure of *Gata1* and *Gata2* genes, and identified hematopoietic enhancer of *Gata1* gene (1997), leukemia due to *Gata1* knockdown (2000), and specific function of GATA-1 N-terminal domain (2001). He received the Gold Prize (1995, Tohoku University) and Inoue Science Prize (1996, The Inoue Foundation) for his contribution to the study of hematopoietic transcription factors.

In 1995, Yamamoto became a Professor at University of Tsukuba. From 1993, he started a series of analyses on NF-E2 and Maf family of transcription factors, and identified the Nrf2-Keap1 pathway regulating the cellular response against electrophilic and oxidative stresses in 1997. Since then, he has been addressing many questions related to this important regulatory pathway. A series of his paper on this topic awarded Thomson Scientific Research Front Award 2004 (Thomson Scientific Co).



Curtis C. Harris, M.D.

Chief, Laboratory of Human Carcinogenesis
National Cancer Institute, NIH
Bethesda, MD, USA

The outstanding scientific contributions of Curtis C. Harris to the fields of molecular carcinogenesis and molecular epidemiology of human cancer, have placed him at the international forefront of cancer research. Harris has received numerous honors throughout his distinguished career and according to ISI Science Watch, March 1998, is one of the 50 most cited biomedical scientists in the 1990's. Recent awards he has received include the Alton Ochsner Award relating Smoking and Health (American College of Physicians), Deichmann Award (International Union of Toxicology), Charles Heidelberger Award (International Society of Gastroenterological Carcinogenesis) and the Distinguished Service Medal, the highest honor of

the U.S. Public Health Service. Curtis C. Harris has generated more than 400 journal publications, 100 book chapters, 10 books and 15 patents. He also serves as an Executive Editor for the journal, Carcinogenesis, and has held or currently holds elected offices in scholarly societies including the American Association of Cancer Research, the International Society of Differentiation, the Keystone Symposium on Molecular and Cellular Biology and the Aspen Cancer Conference.

Curtis C. Harris is the Chief of the Laboratory of Human Carcinogenesis, National Cancer Institute, Bethesda, MD, and Clinical Professor, Division of Clinical Oncology, Georgetown University School of Medicine, Washington, DC, USA

List of Invited Speakers and Participants

Organisers and Invited Speakers

Yinon Ben-Neriah Jerusalem, Israel	Hadassah-Hebrew University Medical Center yinon@cc.huji.ac.il
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Neil D. Perkins Dundee, UK	School of Life Sciences, University of Dundee n.d.perkins@dundee.ac.uk
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■ 2006 CNIO Cancer Conference: Inflammation and Cancer

Hans Schreiber Chicago, USA	University of Chicago hszz@midway.uchicago.edu
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■ 2006 CNIO Cancer Conference: Inflammation and Cancer

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List of Invited Speakers and Participants ■

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Acknowledgements

As a non-profit organisation, we would like to thank our CNIO Cancer Conferences (CCC's) collaborators. Such contribution helps to ensure that our conferences will continue to establish the CNIO as a point of reference for the international cancer research community.



For information about collaboration opportunities, please contact us (ccc@cniio.es)



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Notes

Previous CNIO Cancer Conferences

PREVIOUS CNIO CANCER CONFERENCES

2002

CANCER EPIGENETICS: DNA METHYLATION AND CHROMATIN

ORGANISERS: MANEL ESTELLER (CNIO, MADRID, SPAIN), STEPHEN BAYLIN (THE JOHNS HOPKINS ONCOLOGY CENTER, BALTIMORE, USA)

DATES: MAY 29-31, 2002

THE CELL CYCLE AND CANCER

ORGANISERS: MARCOS MALUMBRES (CNIO, MADRID, SPAIN), CHARLES SHERR (ST. JUDE CHILDREN'S RESEARCH HOSPITAL, MEMPHIS, USA), JIRI BARTEK (INSTITUTE OF CANCER BIOLOGY, DANISH CANCER SOCIETY, COPENHAGEN, DENMARK)

DATES: SEPTEMBER 30 -OCTOBER 2, 2002

MECHANISMS OF INVASION AND METASTASIS

ORGANISERS: JOAN MASSAGUÉ (MEMORIAL SLOAN KETTERING CANCER CENTRE, NEW YORK, USA), RICHARD HYNES (MIT HOWARD HUGHES MEDICAL INSTITUTE, CAMBRIDGE, USA)

DATES: NOVEMBER 18-20, 2002

2003

TARGETED SEARCH FOR ANTICANCER DRUGS

ORGANISERS: AMANCIO CARNERO (CNIO, MADRID, SPAIN), DAVID BEACH (WOLFSON INSTITUTE FOR BIOMEDICAL RESEARCH, LONDON, UK)

DATES: MARCH, 17-19, 2003

SMALL GTPASES IN HUMAN CARCINOGENESIS

ORGANISERS: JUAN CARLOS LACAL (INSTITUTO DE INVESTIGACIONES BIOMÉDICAS, MADRID, SPAIN), CHANNING J. DER (UNIVERSITY OF NORTH CAROLINA, CHAPEL HILL, USA), SHUH NARUMIYA (KYOTO UNIVERSITY, JAPAN)

DATES: JUNE, 16-18, 2003

APOPTOSIS AND CANCER

ORGANISERS: GABRIEL NUÑEZ (UNIVERSITY OF MICHIGAN, ANN ARBOR, USA), MARISOL SOENGAS (UNIVERSITY OF MICHIGAN, ANN ARBOR, USA) AND SCOTT LOWE (COLD SPRING HARBOR LABORATORY, COLD SPRING HARBOR, USA)

DATES: DECEMBER, 1-3, 2003

2004

STRUCTURAL BIOLOGY OF CANCER TARGETS

ORGANISERS: ERNEST LAUE (UNIV. OF CAMBRIDGE, CAMBRIDGE, UK), GUILLERMO MONTOYA (CNIO, MADRID, SPAIN), ALFRED WITTINHOFFER (MAX PLANK INSTITUTE, DORTMUND, GERMANY)

DATES: SEPTEMBER 27-29, 2004

CADHERINS, CATENINS AND CANCER

ORGANISERS: AMPARO CANO (IIB-CSIC, MADRID, SPAIN), HANS CLEVERS (NETHERLANDS INSTITUTE FOR DEVELOPMENTAL BIOLOGY, UTRECHT, THE NETHERLANDS), JOSÉ PALACIOS (CNIO, MADRID, SPAIN), FRANS VAN ROY (GHENT UNIVERSITY, GHENT, BELGIUM)

DATES: NOVEMBER 29-DECEMBER 1, 2004

2005

ANIMAL TUMOUR MODELS AND FUNCTIONAL GENOMICS

ORGANISERS: ALLAN BALMAIN (UCSF COMPREHENSIVE CANCER CENTER, SAN FRANCISCO, USA), MARIANO BARBACID (CNIO, MADRID, SPAIN), ANTON BERNIS (THE NETHERLANDS CANCER INSTITUTE, AMSTERDAM, THE NETHERLANDS), TYLER JACKS (CENTER FOR CANCER RESEARCH, MIT, CAMBRIDGE, USA)

DATES: MARCH 7-9, 2005

MAP KINASES AND CANCER

ORGANISERS: PHILIP COHEN (UNIVERSITY OF DUNDEE, DUNDEE, UK), ROGER DAVIS (UNIVERSITY OF MASSACHUSETTS MEDICAL SCHOOL, WORCESTER, USA), CHRIS MARSHALL (INSTITUTE OF CANCER RESEARCH, LONDON, UK), ANGEL NEBREDÁ (CNIO, MADRID, SPAIN)

DATES: MAY 30 - JUNE 1, 2005

CANCER AND AGING

ORGANISERS: MARÍA BLASCO, CNIO, MADRID, SPAIN; KATHLEEN COLLINS, UCB, BERKELEY, USA, JAN HOEIJMAKERS, ERASMUS UNIVERSITY, ROTTERDAM, THE NETHERLANDS, MANUEL SERRANO, CNIO, MADRID, SPAIN

DATES: NOVEMBER 7-9, 2005

2006

PTEN AND THE AKT ROUTE

ORGANISERS: ANA CARRERA (CENTRO NACIONAL DE BIOTECNOLOGÍA, CSIC, MADRID, SPAIN), PIER PAOLO PANDOLFI (MEMORIAL SLOAN-KETTERING CANCER CENTER, NEW YORK, USA), PETER VOGT (SCRIPPS RESEARCH INSTITUTE, LA JOLLA, USA)

DATES: MAY 8-10, 2006

Forthcoming CNIO Events

FORTHCOMING CNIO CANCER CONFERENCES

(Detailed information will be published at www.cnio.es/cc)

2006

MEDICINAL CHEMISTRY IN ONCOLOGY

ORGANISERS: FERNANDO ALBERICIO (SCIENCE PARK-UNIVERSITY OF BARCELONA, SPAIN), JAMES R. BISCHOFF (CNIO, MADRID, SPAIN), CARLOS GARCÍA-ECHEVERRÍA (NOVARTIS INSTITUTES FOR BIOMEDICAL RESEARCH, BASEL, SWITZERLAND), ANDREW MORTLOCK (ASTRAZENECA PHARMACEUTICALS, MACCLESFIELD, UK)
DATES: OCTOBER 2-4, 2006

TELOMERES AND TELOMERASE

CNIO / JOSEF STEINER CANCER CONFERENCE
ORGANISERS: MARIA BLASCO, CNIO, MADRID, SPAIN; JERRY SHAY, UT SOUTHWESTERN MEDICAL CENTER, DALLAS, USA
DATES: NOVEMBER 13-15, 2006

2007

MOLECULAR MECHANISMS IN LYMPHOID NEOPLASM

ORGANISERS: ELIAS CAMPO, HOSPITAL CLINIC, BARCELONA, RICCARDO DALLA FAVERA, COLUMBIA UNIVERSITY, NEW YORK, USA; ELAINE JAFFE, NCI, BETHESDA, USA; MIGUEL ÁNGEL PIRIS, CNIO, MADRID, SPAIN
DATES: FEBRUARY 19-21, 2007

MYC AND THE TRANSCRIPTIONAL CONTROL OF PROLIFERATION AND ONCOGENESIS

ORGANISERS: ROBERT N. EISENMAN, FRED HUTCHINSON CANCER RESEARCH CENTER, SEATTLE, USA; MARTIN EILERS, UNIVERSITY OF MARBURG, MARBURG, GERMANY; JAVIER LEÓN, UNIVERSIDAD DE CANTABRIA, SANTANDER, SPAIN
DATES: JUNE 11-13, 2007

LINKS BETWEEN CANCER, REPLICATION STRESS AND GENOMIC INTEGRITY. NOVEMBER 5-7

ORGANISERS: OSCAR FERNÁNDEZ-CAPETILLO, CNIO, MADRID, SPAIN; JIRI LUKAS, DANISH CANCER SOCIETY, COPENHAGEN, DENMARK; JUAN MÉNDEZ, CNIO, MADRID, SPAIN; ANDRE NUSSENZWEIG, NCI/NIH, BETHESDA, USA
DATES: NOVEMBER 5-7, 2007

