CNIO Cancer Conference

Targeted Search for Anti-Cancer Drugs

Madrid, March 17-19, 2003
SPANISH NATIONAL CANCER CENTRE

Organisers:
Amancio Carnero and David H. Beach

Auditorium CNIO
Centro Nacional de Investigaciones Oncológicas
Melchor Fernández Almagro, 3
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A compilation of short biographies of organisers and speakers in accordance with the order of the scientific programme.

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**Forthcoming CNIO activities**
Dear Colleague,

We would like to welcome you to the CNIO Cancer Conference (CCC) on Targeted Search for Anti-Cancer Drugs.

This conference is following the trend being established through the CCC’s: to bring together the very top scientists in a given field related to cancer and to provide the best possible forum for discussion. We are confident that collectively the CNIO Cancer Conferences are of great interest to the scientific community and attract international attention to the CNIO.

At the CNIO Cancer Conferences we emphasise a workshop ambience, thus CNIO scientists will be able to follow the conference from our seminar rooms in order to keep the number of participants to the necessary minimum.

We very much hope that you enjoy this exciting conference.

With our personal thanks,

Amancio Carnero  
Centro Nacional de Investigaciones Oncológicas  
Madrid, Spain

David H. Beach  
Genetica, Inc  
Boston, USA

As the newest member of the European Cancer community, the CNIO is very much open to establishing strong collaborations with you and your respective organisations. We would therefore be delighted to inform you about our Scientific Strategic Plan for the next few years (the CNIO will not be fully staffed until 2006), and to show you our facilities. Should you wish to meet with any member of our Faculty, please let us know and we will be delighted to introduce you.
**Targeted Search for Anti-Cancer Drugs**

Auditorium of the Spanish National Cancer Centre, CNIO (Melchor Fernández Almagro, 3, E-28029 Madrid)  
March 17-19, 2003

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* **CNIO Building Tour:** following directly on from the close of Monday’s sessions, a short Tour will be conducted by CNIO staff for participants interested in CNIO activities. The meeting point will be at the Registration Desk.

**Lunches:** Lunch will be provided, courtesy of the CNIO, in the main dining room of the building.
Detailed Programme

Monday, March 17, 2003

Welcome address
9:30-9:45  M. Barbacid / Centro Nacional de Investigaciones Oncológicas. Madrid, Spain

Session I: Drug Design
Chair: D. H. Beach

9:45-10:15  R. Abagyan / The Scripps Research Institute, La Jolla, USA
Docking and Virtual Screening in Lead Drug Discovery

10:15-10:45  T. Blundell / University of Cambridge, UK

10:45-11:00  G. Montoya / Centro Nacional de Investigaciones Oncológicas, Madrid, Spain
Short talk
Structural biology of methyl DNA binding proteins

11:00-11:30  Coffee Break

11:30-12:00  P. M. Fischer / Cyclacel Ltd., Dundee, UK
Discovery and development of pharmaceutical cell-cycle modulating agents

12:00-12:30  P. Workman / Cancer Research UK, Centre for Cancer Therapeutics, Sutton, UK
Combinatorial attack on multiple oncogenic pathways: Targeting the Hsp90 molecular chaperone

12:30-14:30  Lunch-Break
**Session II: Preclinical models**  
Chair: A. Ullrich  
14:30-15:00 **M. Barbacid** / Centro Nacional de Investigaciones Oncológicas, Madrid, Spain  
Functional Genomics in Mice: Target Validation and Tumour Models  
15:00-15:30 **J. Piulats** / Merck Farma y Química, S.A., Barcelona, Spain  
Targets for an anti-angiogenic approach in cancer therapy  
15:30-16:15 Coffee-Break/Poster viewing  
16:15-16:30 **A. Pandiella** / Instituto de Microbiologia Bioquimica-CSIC, Salamanca, Spain  
Short talk  
Screening for agents that inhibit the Erk5 MAPK  
16:30-17:00 **S. Lowe** / Cold Spring Harbor Laboratory, USA  
Genetics of drug sensitivity and resistance in a mouse lymphoma model

**Tuesday, March 18, 2003**

**Session III: Genetic Search of new targets**  
Chair: S. Lowe  
9:30-10:00 **D.H. Beach** / Genetica inc, Boston, USA  
Cellular Immortalization and the Warburg Effect  
10:00-10:30 **A. Gudkov** / Lerner Research Institute, Cleveland, USA  
SSA: a universal functional genetic approach to prospective drug targets  
10:30-10:45 **A. Gartel** / University of Illinois at Chicago, USA  
Short talk  
A new strategy for identification of proapoptotic compounds for destruction of tumor cells  
10:45-11:30 Coffee-Break/Poster viewing  
11:30-12:00 **R. Agami** / The Netherlands Cancer Institute, Amsterdam, The Netherlands  
Studying Cancer through Stable Inhibition of Gene Expression by RNA Interference  
12:00-12:30 **B.B. Zhou** / Incyte Genomics, Newark, USA  
Drug Discovery Targeting Checkpoint Pathways: Chemosensitization vs Chemoprotection  
12:30-13:00 **C.B. Thompson** / University of Pennsylvania, Philadelphia, USA  
Akt As a Molecular Target  
13:00-14:30 Lunch Break
Session IV  Therapeutic Strategies
Chair: G. Powis

14:30-15:00  L. Meijer / Centre National de la Reserche Scientifique, Roscoff, France
Pharmacological Inhibitors of Cyclin-Dependent Kinases (CDKs) and Glycogen Synthase Kinase -3 (GSK-3)

15:00-15:30  N. Tonks / Cold Spring Harbor Laboratory, USA
From structure to function of protein tyrosine phosphatases

15:30-15:45  L. Kirkpatrick / ProlX Pharmaceuticals, Tucson, USA
Short talk  Thioredoxin a novel target for cancer drug action:
PX-12 a thioredoxin inhibitor in a Phase 1 clinical Trial

15:45-16:15  Coffee-Break/Poster viewing

16:30-17:00  B. Burgering / University Medical Center Utrecht, Utrecht, The Netherlands
Cell cycle and death control: Long live Forkhead

Wednesday, March 19, 2003

Session V: Therapeutic Strategies
Chair: R. Abagyan

9:30-10:00  L. H. Hurley / Arizona Cancer Center, Tucson, USA
The Role of Secondary DNA Structures in Silencing Transcription

10:00-10:30  G. Powis / Arizona Cancer Center, Tucson, USA
Hypoxia inducible factor-1α (HIF-1α) as a novel target for cancer drug development:
PX-478 an antitumor inhibitor of HIF-1α

10:30-11:00  Coffee-Break

11:00-11:30  J.C. Lacal / Instituto de Investigaciones Biomédicas, CSIC, Madrid, Spain
Choline kinase is a new target for cancer therapy: when, why and how chok inhibitors work as specific antitumor drugs

11:30-12:00  A. Ullrich / Max-Planck Institut for Biochemistry, Martinsried, Germany
From Gene to Therapy

12:00-12:05  Concluding remarks
Posters (in alphabetical order of presenting author)

Effects of Lycopene on Proliferation of Human Breast Cancer T47D cells and its Tamoxifen Resistant subtype
Ebrahim Azizi, Tehran Univ. of Med. Sciences (TUMS), Tehran, Iran

Serum pyrrolidon carboxypeptidase activity in N-methyl nitrosourea induced rat breast cancer.
M. Pilar Carrera, Universidad de Jaén, Spain

Inositol Pentakisphosphate Promotes Apoptosis through the PI 3-K/Akt Pathway
Marco Falasca, The Sackler Institute, University College London, London, UK

Purine based inhibitors of cyclin-dependent kinases
Vladimir Krystof, Palacky University, Olomouc, Czech Republic

Prodigiosin, a new proapoptotic drug: dna interaction and topoisomerase I inhibition
Ricardo Pérez-Tomás, Universitat de Barcelona, Spain

Chemical Genetic Approaches to Selective Inhibitors of Histone Deacetylases
Lucy Pérez Fernández, Harvard University, Cambridge, USA

Inhibition of Choline Kinase as a specific cytotoxic strategy in H-Ras transformed cells
Agustín Rodríguez-González, Instituto de Investigaciones Biomédicas (CSIC), Madrid, Spain
Abstracts-Sessions
Docking and Virtual Screening in Lead Drug Discovery

Ruben Abagyan

Department of Molecular Biology, The Scripps Research Institute, La Jolla, USA

Advanced modeling by homology techniques can be employed to generate 3D models for most of the interesting new gene family members. This opens many new opportunities for structural structure based functional annotation and quick identification of lead compounds via flexible docking and virtual ligand screening.

First, we have developed two new techniques to assign rational drug design using crystallographic structures or models by homology. The binding pockets can be automatically identified even though the native ligand is unknown. This algorithm has been tested on over 10,000 complexes. We have also built a comprehensive database of protein pockets and clustered them into families.

Second, a deformed ligand binding pocket in a model by homology can be refined by explicit global optimization of one or several known ligands and surrounding receptor side-chains.

Third, a procedure is described to identify a native ligand from a collection of all known biological substrates. The procedure was also applied to some receptors including GPCRs.

Finally, new computational technology for virtual ligand screening allows to generate alternative receptor conformations and perform flexible docking of hundreds of thousands of virtual compounds to the binding site.

The success of this technology is demonstrated on several benchmarks and experimental lead discovery projects. Using ICM docking and scoring technology we have identified new ligands using, in most cases, only models by homology. Some of the recent results tested experimentally in collaboration with Drs. Herbert Samuels (NYU), Xiaokun Cheng (Burnham), Dimitar Nikolov (Sloan Kettering) Dr. Maxim Totrov (Molsoft) and Dr. Matthieu Schapira (Molsoft) include: de novo design of novel antagonists of RAR and thyroid hormone receptor; de novo design of ligands targeting Ephrin-Ephrin receptor interactions; de novo discovery of ligands of the TR3 orphan nuclear receptor.
The structural biology of multiprotein complexes of cell regulation and repair: applications to drug discovery

Tom L. Blundell
Department of Biochemistry, University of Cambridge, Cambridge, UK

Multiprotein complexes mediate most processes of cell regulation and repair. Understanding how weak binary interactions can lead through synergy to specificity and stability in multiprotein systems is central to regulation of cellular processes. We have addressed this question by defining by X-ray analysis the 3-D structures of multiprotein complexes involved in extra-cellular, cytoplasmic, and nuclear signalling and regulation.

In this lecture, I will survey work from our laboratory on four different systems. These include structural biology of:

- protein kinases: cyclin D-dependent kinase Cdk6 bound to the cell cycle inhibitor p19\(^{INK4d}\) (Brotherton et al. (1998) Nature 395, 244-250).
- non-homologous end joining systems including an Xrcc4 dimer in complex with DNA ligase IV. (Sibanda et al. (2001) Nature Structural Biology, 8, 1015-1019)
- homologous recombination involving BRCA2 repeats and rad51 (Pellegrini et al. (2002) Nature 420, 287-293)

I will compare the interacting surfaces in these regulatory complexes with those in other protein complexes and discuss their relevance to accurate transduction of signals. I will also discuss new approaches to drug discovery involving high-throughput drug discovery based on such structural information.
DNA methylation is the major modification of eukaryotic genomes and plays an essential role in mammalian development. Human proteins MECP2, MBD1, MBD2, MBD3, and MBD4 comprise a family of nuclear proteins related by the presence in each of a methyl-CpG binding domain (MBD). Each of these proteins, with the exception of MBD3, is capable of binding specifically to methylated DNA. Furthermore CpG methylation, is associated with transcriptional repression and has been implicated in cancer. The determination of the crystal structure of proteins of this family in complex with methylated DNA will provide a source of key information to understand the relevance of mutations in the interaction with DNA and other proteins and their relationships with oncogenic processes. During this talk a brief report about our efforts to obtain the structure of some of the members of this family will be discussed.
Discovery and Development of Pharmaceutical Cell-Cycle Modulating Agents

Peter M. Fischer
Cyclacel Limited, Dundee, Scotland, UK

Human tumours are characterized by numerous genetic and functional abnormalities, particularly in the pRb and p53 pathways, that permit transformed cells to escape the controls over progression through the cell division cycle present in normal proliferating cells. Underlying the rationale for the search and development of modern mechanism-based anti-cancer drugs has been the expectation that pharmacological inhibition of selected molecular targets should be able not only to restore cell cycle checkpoint control, but to lead to selective killing of cancer cells.

One such group of molecular targets is represented by the CDKs. High levels of E2F transcriptional activity, which is observed in tumour cells with pRb-pathway mutations, in conjunction with the pro-apoptotic effects of E2F1, provides a mechanistic reason why pharmacological inhibition of CDK2 activity, which is required for terminating E2F1 transcriptional activity, should kill tumour cells selectively. CYC202 (a chirally pure form of the 2,6,9-trisubstituted purine R-roscovitine) is a potent and comparatively selective inhibitor of CDK2 capable of inducing apoptosis in tumour cells and ablating tumour progression in xenograft models. Phase I clinical evaluation of this pharmaceutical agent is nearing completion and the preliminary conclusion is that it is well tolerated at orally administered doses that result in potentially bioactive physiological concentrations. Phase II trials, designed to explore safety, PK profile, and anti-tumour activity, as well as the effect on biomarkers, of the combination of CYC202 and chemotherapy, are also now under way. A group of potential follow-on compounds from a different chemical class and representing an alternative pharmacophore, i.e. 4-heteroaryl-2-anilino-pyrimidines, was identified initially through virtual screening; structure- and PK-based design has been used to develop potent candidate molecules with appreciable in vivo anti-tumour activity. As an alternative to ATP antagonism, CDK2 inhibition can be effected through blocking of the macromolecular substrate binding site on the CDK2 activating cyclin E (G1-S transition) and cyclin A (S-phase) subunits. Peptide minimization and optimization studies, in conjunction with a detailed structural understanding from X-ray crystallographic analysis of relevant complexes, suggest that pharmacological cyclin groove inhibitors might be arrived at through peptidomimetic design.

Tumour cells also very frequently circumvent the p53-associated regulatory network that guards over continued cellular integrity, by disabling the function of p53, either through mutation of p53 directly, or frequently by over-expression of its negative regulator MDM2. In either case, inhibition of the MDM2 interactions with p53 or E2F1 may lead to selective tumour cell apoptosis. Starting from the structurally known molecular interaction between MDM2 and peptides derived from p53, and using biochemical, cellular, and NMR-based structural screening methods, small molecules were identified that represent a starting point for the design and optimization of pharmacological MDM2 inhibitors.
Combinatorial attack on multiple oncogenic pathways: Targeting the Hsp90 molecular chaperone

Paul Workman

Cancer Research UK Centre for Cancer Therapeutics, Institute of Cancer Research, Sutton, UK

Hsp90 is a molecular chaperone that is overexpressed in cancer cells and is essential for the folding stability and functional activity of many oncogenic 'client' proteins, including Raf-1, ErbB2, Akt, Bcr-Abl, Cdk4, Polo-1, Met, mutant p53, Hif-1a, estrogen/androgen receptors and the catalytic subunit of telomerase hTERT. Inhibition of Hsp90 would provide combinatorial blockade of a range of oncogenic pathways and block all six hallmark traits of cancer. The development of Hsp90 inhibitors will be described, together with experiments to investigate the molecular pharmacology of these agents. The benzoquinone ansamycin 17-allylamino, demethoxygeldanamycin (17AAG) inhibits both the Ras → Raf → Mek → Erk pathway and the PI3 kinase → PDK1 → Akt pathway leading to G1/G2M cell cycle arrest and apoptosis in cancer cells and also at prolonged growth delays in human tumour xenografts. A molecular signature of Hsp90 inhibition has been defined by gene expression microarrays and proteomics. We have used this signature this in our Phase 1 clinical trial of 17AAG and obtained, evidence of Hsp90 inhibition was obtained in peripheral blood lymphocytes and tumour biopsies, together with indications of disease stabilization. Novel inhibitors of Hsp90 have been identified by high throughput screening and these are being optimised by rational drug design based on the x-ray crystal structure of Hsp90. Recent work has identified Aha1 as a co-chaperone that activates the ATPase activity of Hsp90 and is upregulated by Hsp90 inhibitors. The latest results on the molecular mode of action and development of Hsp90 inhibitors will be described.
Mariano Barbacid, Carmen Guerra, Victoria Campuzano, Juan Velasco, Nieves Mijimolle and Alma Dhawahir

Molecular Oncology Programme, Centro Nacional de Investigaciones Oncológicas, Madrid, Spain

The development of homologous recombination techniques in mouse embryonic stem (ES) cells is making possible to use classical reverse genetics strategies to analyse gene function in mammals. Yet, the somatic nature of most cancer-causing mutations requires development of sophisticated gene-targeting strategies that allow introduction of the desired mutation(s) in a spatially and temporally controlled manner. We are currently using such gene-targeted mice to:

(i) validate farnesyl transferase (FT) as a target for the development of anti-cancer drugs
(ii) generate a tumour model in which the endogenous K-Ras gene can be activated as an oncogene in a controlled manner in specific somatic cells and tissues.

Mouse embryos lacking FT activity die during early embryonic development. Analysis of females at 6.5 dpc indicate that FT-deficient embryos implant but their inner cell mass (ICM) does not develop. Likewise, FT (−/−) blastocysts do not proliferate in culture beyond the E6.5 stage, suggesting that FT activity is essential for early embryonic cell proliferation. To ablate FT in adult tissues, we have generated mice (R-ERT strain) that express an inducible CreERT recombinase in a ubiquitous fashion by inserting an IRES-CreERT cassette at the 3’ end of the gene encoding the large subunit of RNA polimerase II by homologous recombination. Offspring derived from mating FT conditional KO mice with R-ERT animals were submitted to systemic exposure of 4-OH-tamoxifen. This treatment result in complete ablation of the FT locus as determined by lack of detection of the floxed FT allele by PCR analysis, except in muscle and brain. These FT KO adult mice survive without obvious abnormalities at least for six months, indicating that FT activity is no longer essential in adult tissues. However, they are sensitive to bleeding stress suggesting a defect in the regeneration of hematopoietic cells. These animals will be submitted to tumourigenesis protocols before and after FT ablation to validate this enzyme as a suitable target for the development of anti-tumor drugs.

We have used a similar strategy to generate mice, K-Ras (+/V12), that carry an endogenous K-Ras oncogene that can only be expressed in the presence of an active Cre recombinase. These mice also carry a second gene-targeting event that allows co-expression of a colour marker (Lac Z) in a bicistronic fashion. Systemic treatment of K-Ras (+/V12);(R-ERT) mice with 4-OH-tamoxifen results in the activation of the endogenous K-Ras oncogene in multiple cell types throughout the body. Yet, we have only detected abnormally proliferating cells in lung adenomas several months after steroid treatment. This tumour model should allow us to dissect the multi-step process of carcinogenesis in an in vivo setting that closely resembles activation of K-Ras oncogenes in cancer patients. Moreover, it should be useful to evaluate inhibitors of the Ras pathway as anti-tumour drugs.
Targets for an anti-angiogenic approach in cancer therapy

Jaume Piulats

Departamento de Inmunología, University of Barcelona, and Laboratorio de Bioinvestigación de Merck, Barcelona, Spain

In 2001 Hanahan and Weinberg (Cell 100, 57-70 (2001)) proposed six hallmarks of cancer disease which can be shared by all types of neoplastic disorders. One of these hallmarks is the sustained process of angiogenesis induced by the proangiogenic factors secreted by the tumor cells. Currently, the inhibition of tumor angiogenesis is an important approach for cancer therapy. In fact, this goal was already proposed by Folkman in the beginning of the seventies. Unfortunately, at this time our knowledge on the biochemical and physiological mechanisms which direct the neovascularization was very poor and, consequently, we had to wait thirty years until we have collected enough scientific data for proposing new therapeutic targets. Nevertheless, the switch of tumor cells to an angiogenic phenotype is a complex process which is far to be modulated by a single pharmacological agent. During our presentation we will analyze the current situation of antiangiogenic therapy reviewing the new available drugs as well as the agents which will be briefly launched.

Currently, a wide spectrum of potential therapeutic targets are under intensive research, therefore, this situation already indicates the difficulties for a pharmacological modulation of tumor angiogenesis using one unique target, and one unique agent.

Our group has focused its efforts in the study of the role of $\alpha_v\beta_3$ integrin (vitronectin receptor) in angiogenesis process. During this study, new integrin antagonists which will be reviewed have been generated. We would like to emphasize on a new agent, the monoclonal antibody 17E6 (anti-$\alpha_v$), which has showed a very promising preclinical profile. This monoclonal showed a significant antitumoral effect on $\alpha_v$ positive experimental tumors as well as antiangiogenic activity in a set of in vitro and in vivo models. The variable regions of 17E6 have been deimmunized by removing the T-cell epitopes and finally humanized with a human IgG2 construction. The properties of this monoclonal will be analized during the presentation.

The challenge for antiangiogenic therapy will be how to adapt to the clinical practice the current knowledge about the pharmacological activity of new agents. And, viceversa, how to design new experimental models for achieving an improved translational research.
Screening for agents that inhibit the Erk5 MAPK

Atanasio Pandiella, and Juan Carlos Montero

Instituto de Microbiología Bioquímica, CSIC-Universidad de Salamanca, Salamanca, Spain

We searched a library of chemical compounds known to inhibit cell proliferation, and unpurified bacterial cell extracts or culture media for their ability to inhibit different MAPK routes. Of 120 chemically pure compounds and 400 bacterial extracts and culture media a 5% proportion of the agents or bacterial mixtures were found to contain products that inhibited both the Erk1/2 and the Erk5 routes. Their action appeared specific for these MAPKs since these products did not affect the kinase activity or transautophosphorylation of the epidermal growth factor receptor (EGFR). Further analyses led to the identification of four compounds that specifically inhibited the Erk5 route without affecting Erk1/2 upon EGFR activation in HeLa cells. Since the Erk5 kinase was previously found to be constitutively active in breast cancer cells overexpressing ErbB2, and the action of Erk5 was required for cell proliferation induced by this receptor, the identification of agents that specifically target this route may be of benefit in the control of tumors that bear alterations in the ErbB receptors.

Note: This project has been performed in collaboration with Biomar S.L. which provided cell extracts, bacterial media, and chemically pure compounds.
Genetics of drug sensitivity and resistance in a mouse lymphoma model

Scott W. Lowe
Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, USA

Although many anticancer agents are known to damage DNA, the molecular determinants of treatment sensitivity remain poorly understood. Conventional approaches to identify these factors rely on human tumor cell lines treated in vitro or as ectopic xenographs. As an alternative approach, we are using transgenic mouse models to study drug action in spontaneous tumors treated at their natural site. Primary B cell lymphomas, arising in Eµ-myc transgenic mice with short latency and high penetrance, resemble closely the clinicopathological pattern of human non-Hodgkin’s lymphoma and can be treated with various anticancer therapies. We will describe methods to evaluate the short and long-term responses of Eµ-myc lymphomas to anticancer treatments in vivo. Also, we will outline strategies to generate primary lymphomas with specific genetic lesions, and illustrate how such genetically controlled tumors can be used to understand the contribution of specific genes (e.g. p53) or processes (e.g. apoptosis, senescence) to treatment sensitivity. By comparing results from our in vivo system to more conventional assays, we will show that some determinants of treatment sensitivity are missed in vitro or when using established cell lines. Finally, we show recent results demonstrating that stable RNA interference technology can be used to suppress gene function in vivo, allowing analysis of loss of function phenotypes during lymphoma development and therapy. We expect that the Em-myc lymphoma model and other physiologic test systems will improve our understanding of drug action, and will provide relevant experimental conditions to test compounds directed against specific genetic lesions.
Cellular Immortalization and the Warburg Effect

Hiroshi Kondoh, Matilde E. Lleonart, Jing Wang, Joanne Crossley, Mark Clement, Amancio Carnero, David H. Beach
Genetica Inc. Boston, USA

Glycolysis, an essential energy source for many cells, results in the conversion of glucose into pyruvate through ten enzymatic reactions. Pyruvate can be utilized in TCA cycle to generate ATP in mitochondria. Most tumors have altered metabolic profiles and show enhanced glycolysis, historically reported by Warburg over seven decades ago. Indeed, positron-emission tomography (PET) studies with 2-[^18F]fluoro-2-deoxy-D-glucose in increasingly used clinically to physically locate tumors with high rates of glycolysis. In cancer cells, the activities of several glycolytic enzymes are significantly increased, including hexokinase, phosphofructokinase, and pyruvate kinase. Oncogenes such as ras, src, myc can enhance glycolysis by increasing the expression of glucose transporters and glycolytic enzymes. These metabolic change might hypothetically confer a growth advantage, especially for solid tumors that are partially hypoxic. However, it is unclear whether enhanced glycolysis, although very widely described, has a direct role in tumourigenesis.

We have used mouse embryonic fibroblasts (MEF) to study replicative senescence in vitro. Using a retroviral cDNA library based on the MarX vector, we screened for genes which can confer immortality. Among those identified, we found that twofold overexpression of Phosphoglycerate mutase (PGM), one of the glycolytic enzymes, can reversibly immortalise MEF. Both forms of PGM, so-called muscle and brain specific isozymes, have similar activity, but not phosphofructokinase, another glycolytic enzyme. Active site mutations in PGM do not immortalize and generally induce premature senescence. In addition reduced wildtype PGM expression conferred by siRNA also induces premature senescence in primary or p53 dominant-negative immortalised MEF. Finally we found in several cancer cell lines, PGM inactivation can cause growth retardation or premature senescence. These observations suggest that high rates of glycolysis may play an active role in aspects of tumourigenesis.
SSA: a universal functional genetic approach to prospective drug targets

Andrei V. Gudkov

Department of Molecular Biology, Lerner Research Institute, Cleveland Clinic Foundation, Cleveland, Ohio, USA

An ideal drug discovery pipeline involves identification of drug targets by functional genetics followed by creation of smart readout systems and screening of chemical libraries. Prospective drug target can be found among cellular factors, the suppression of which leads to a desirable phenotype (that in cancer treatment field is death or growth inhibition of tumor cells). Drug discovery process could be faster if it would be possible to directly identify genes that fit this definition. However, the ability to identify genes for putative drug targets by functional selection has traditionally been a difficult rate-limiting stage in drug discovery process because of two major reasons: (i) difficulties in designing genetic selections based on gene repression and (ii) lack of techniques allowing for negative selection, i.e. isolation of clones that have detrimental effect on cell growth or viability. We suggested practical solutions for both of these problems by developing two gene screening techniques: the genetic suppressor element (GSE) methodology and selection-subtraction approach (SSA). While GSE technique provides the way to generate libraries enriched with gene-specific inhibitory clones (libraries of randomly fragmented cDNAs encoding antisense RNAs or truncated proteins with dominant negative activity), SSA makes it possible to screen expression libraries for growth inhibitory or killing clones. SSA is based on simultaneous monitoring of relative abundance of all library clones in library-transduced target cells followed by isolation of those genetic elements that change their relative representation as a result of their effect on cell growth or viability. Besides gene discovery applications, SSA offers an effective one-step procedure for isolation of biologically active peptides derived from important regulatory proteins and generation of mutants with the desirable properties, including temperature sensitive and dominant negative ones. Application of a combination of GSE and SSA techniques to identification and analysis of targets within p53 signaling pathway will be described.
A new strategy for identification of proapoptotic compounds for destruction of tumor cells

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The cyclin-dependent kinase inhibitor p21 (Waf1/Cip1) is a negative regulator of the cell cycle. There is a mounting evidence that p21 is also a general inhibitor of programmed cell death, which is important for successful elimination of breast cancer cells by chemotherapy and radiation. The HER-2/neu gene encodes 185 kDa (p185) transmembrane receptor tyrosine kinase, and it was found to be amplified or overexpressed in up to 30% of human breast carcinomas. Overexpression of the HER-2/neu gene correlated with poor prognosis and lower overall survival rate. Taxol is a highly effective antineoplastic agent for the treatment of metastatic breast cancers. HER-2/neu overexpression confers increased resistance of breast cancer cells to Taxol-induced apoptosis by transcriptional upregulation of CDK inhibitor p21 (WAF1/CIP1). We propose a strategy to identify chemical inhibitor of the p21 gene transcription by screening of individual compounds of chemical libraries. Chemical inhibitors of the p21 gene transcription that will increase tumor cell death in response to chemotherapeutic agents. We constructed human colon cancer cell line LIM1215 with the bacterial LacZ gene under control of the human p21 promoter, which is inducible by adriamycin via a p53-dependent mechanism. Following addition of adriamycin, this cell line will be used for identifying of a chemical inhibitors of p21 transcription by screening of individual compounds of a chemical NCI library and selecting compounds that downregulate -Gal expression. Inhibitors of p21 transcription isolated from this screening will represent two classes of chemicals, specific repressors of the p21 promoter and general inhibitors of p53 function. To identify true repressors of the p21 promoter these compounds will be re-screened in the LIM1215 cell line has the LacZ gene under a minimal heat shock promoter located downstream of multiple p53-binding sites, and shows strong p53-dependent induction of LacZ in response to DNA damage. Only compounds that repress p53-dependent activation of p21, but do not affect p53-dependent activation of LacZ, will be selected for further evaluation. We hypothesize that the administration of such inhibitors of p21 transcription in combination with Taxol in breast carcinomas with overexpression of the HER-2/neu will promote destruction of tumor cells and improve their response rate to Taxol. Identified transcriptional inhibitors of p21 may be used in combination with different chemotherapeutic drugs for treatment of breast cancer.
Studying Cancer Through Stable inhibition of Gene Expression by RNA interference

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Cancer development and progression require concerted action of multiple genetic alterations such as appearance of onco-genes, inactivation of tumor suppressor genes and telomere maintenance. To study each of these events we have developed a novel vector system, named pSUPER, which directs persistent and specific inhibition of gene expression in human somatic cells through RNA interference (RNAi). We use this system to target oncogenic K-RAS V12 without affecting its wild type counterpart and show that this leads to loss of anchorage-independent growth and tumorigenicity. We also use primary human cells and target putative tumor suppressor genes to examine their role in cancer development. Altogether, the use of vectors to inhibit gene expression by RNAi enables us to study and identify important cancer related events and develop tumor-specific therapeutic tools to reverse the tumor phenotype.
Drug Discovery Targeting Checkpoint Pathways: Chemosensitization vs Chemoprotection.

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Tumors respond differently from normal cells to DNA damaging agents and tubulin poisons. The molecular mechanisms of cellular responses to these anti-cancer agents have begun to be unraveled. DNA damage response include not only checkpoint and apoptosis, but also direct activation of DNA repair networks. Many tumors are defective in G1/S checkpoint, but maintain much of G2/M checkpoint. Downstream in the DNA damage response pathway, Chk1 is a checkpoint kinase regulating the G2/M checkpoint. Both dominant negative and small molecule tool compound have suggested Chk1 as a chemosensitization target, but checkpoint abrogation probably is not sufficient for the chemosensitization effect. On the other hand, recent knockout studies demonstrated that tumor suppressor Chk2 regulates the DNA damage induced apoptosis through p53 dependent transcription and suggested Chk2 as a chemoprotection target. Drugs targeting Chk1 and Chk2 have the potential to significantly improve the therapeutic windows of DNA damaging agents available in clinics.

The cellular response to tubulin poisons include spindle checkpoints and a prophase checkpoint depending on Chfr. Chfr is an ubiquitin ligase in vitro and in vivo. The RING-finger domain of Chfr is required for its ligase activity and its checkpoint function. In addition, Chfr expression increases cellular survival after treatments with tubulin poisons. Since Chfr is active in primary cell lines but defective in 50% of tumor cell lines examined so far, it could represent one of the genes whose status affect tumor’s sensitivity towards tubulin poison agents.
Akt As a Molecular Target

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Constitutive activity of the serine/threonine kinase Akt is one of the most frequent perturbations displayed by cancer cells. To understand the contribution of this kinase to tumorigenesis the effects of Akt activation were studied in a non-transformed hematopoietic cell line. Constitutive activity of Akt was sufficient to promote the leukemic transformation of these cells in mice. Surprisingly, Akt did not promote the proliferation of these cells in culture. Rather, Akt caused a dramatic increase in glucose consumption by the cells. Glucose was utilized in excess of cellular demand as indicated by the increased production of lactate waste, and Akt cells maintained higher rates of glycolysis despite unchanged oxygen consumption. The specific stimulation of proximal glucose metabolism by Akt was confirmed by measurements of intracellular NADH pools. In the murine leukemia model, maintenance of Akt activation was required to sustain elevated rates of glucose capture in vivo. Maintenance of Akt activity had a more pronounced effect on glucose metabolism than on proliferation or survival in the leukemic cells. These results suggest that Akt activity may explain the elevated rates of aerobic glycolysis long noted to characterize cancer cells and underlying the clinical utility of FDG-PET scanning. Molecular targeting of Akt may represent a novel therapeutic strategy to reverse the altered metabolism of cancer cells.
Pharmacological Inhibitors of Cyclin-Dependent Kinases (CDKs) and Glycogen Synthase Kinase -3 (GSK-3)

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Cyclin-dependent kinases (CDKs) regulate the cell division cycle, apoptosis, transcription, differentiation, as well as functions in the nervous system. GSK-3, an essential element of the WNT signaling pathway, is involved in multiple physiological processes including cell cycle regulation by controlling the levels of cyclin D1 and β-catenin, dorso-ventral patterning during development, insulin action on glycogen synthesis, axonal outgrowth, HIV-1 Tat-mediated neurotoxicity, and phosphorylation of tau, a characteristic of Alzheimer’s disease.

Deregulation of CDKs and GSK-3 in various diseases has stimulated an intensive search for selective pharmacological inhibitors. Over fifty CDK inhibitors and about ten GSK-3 inhibitors have been identified, among which more than twenty have been co-crystallized with CDK2 and one with GSK-3. They all target the ATP-binding pocket of the catalytic site of the kinases. The actual selectivity of most compounds, and thus the underlying mechanism of their cellular effects, is poorly known. Affinity chromatography using immobilized inhibitors provides one approach to identify the actual targets of kinase inhibitors. Pharmacological inhibitors of CDKs and GSK-3 are currently being evaluated for therapeutic use against cancer, neurodegenerative disorders (Alzheimer’s disease, Parkinson’s disease, stroke, …etc.), cardiovascular disorders (atherosclerosis, restenosis), glomerulonephritis, viral infections (HCMV/HIV/HSV) and parasitic protozoa (Plasmodium, Leishmania). The development of these inhibitors against cancer will be presented with two examples, roscovitine and indirubins.

Reversible phosphorylation of tyrosyl residues in proteins, controlled by the coordinated actions of Protein Tyrosine Kinases and Protein Tyrosine Phosphatases (PTPs), is of fundamental importance in the regulation of cellular signalling pathways. Links between dysfunctional tyrosine phosphorylation and human disease, including cancer, have been established, with PTPs becoming a focus of study in this area. There are ~100 PTP genes in the human genome. Although there are data to illustrate the importance of select PTPs in regulating signal transduction under normal and pathophysiological conditions, the majority of these enzymes are known only by their sequence. A current challenge is to develop strategies to explore PTP function. Crystal structures of several PTPs have been determined and have yielded crucial insights into substrate specificity, regulation and function. We have developed “substrate-trapping” mutant PTPs that retain the ability to bind substrates with high affinity, both in vitro and in vivo, but fail to catalyse efficient dephosphorylation and have used these mutants to show that PTPs display exquisite substrate selectivity in a cellular context. We have demonstrated that the receptor PTP DEP-1, which has been implicated in the regulation of growth, differentiation and transformation, has the potential to recognise particular tyrosine phosphorylation sites within the PTK Met, which is a regulator of mitogenesis, morphogenesis and migration. Therefore, DEP-1 may function normally in controlling the specificity of signals induced by Met. Furthermore, down-regulation of DEP-1, which is mutated in colon, lung and breast cancer, may be coupled with up-regulation of Met function in the progression of certain human cancers. It is also becoming apparent that PTPs are subject to regulation of activity by covalent modification, including at the level of reversible oxidation. The active site of members of the PTP family is characterized by the presence of an invariant Cys residue that functions as a nucleophile in catalysis and, due to the unique environment of the catalytic centre, is exquisitely sensitive to oxidation. Therefore, the production of reactive oxygen species (ROS) in response to a variety of signals, including mitogenic stimuli, may augment tyrosine phosphorylation in part through transient oxidation of this Cys residue with concomitant inhibition of PTP function. We propose that stimulus-induced oxidation may be used as a means of “tagging” and identifying those PTPs that provide inhibitory constraint upon the signalling response triggered by that stimulus, thereby revealing important insights into PTP function. In this talk, I will discuss some of our recent studies in this area.
Thioredoxin a novel target for cancer drug action: PX-12 a thioredoxin inhibitor in a Phase 1 clinical Trial

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Thioredoxin, a small redox protein that inhibits apoptosis, stimulates cellular proliferation and has been found to be over expressed in a number of human tumors, including lung, colon and gastric. High levels of thioredoxin in human lung and colon tumors are associated with poor patient prognosis. PX-12 is a small molecule inhibitor of thioredoxin and the first agent of this class to be tested in clinical trials. It is a potent stimulator of apoptosis and had been found to have good anti-tumor activity in a variety of human tumor xenografts in animal models. PX-12 also inhibits the thioredoxin enhancement of hypoxia inducible factor-1a (HIF-1a) and VEGF production by tumors and leads to decreased tumor angiogenesis. PX-12 is under evaluation in a Phase 1 clinical trial. The objectives of this trial are to determine the maximum tolerated dose (MTD) of PX-12 and to assess its pharmacokinetic and pharmacodynamic profiles in patients with advanced malignancies who had failed standard therapy. PX-12 was delivered as an infusion over 1 or 3 hr daily for 5 days every 21 days. As of January 2003, 23 patients have been enrolled and the 96 mg/m²/day cohort has been completed with only 1 grade 2 drug related cough noted. Pharmacokinetic and dynamic samples have been collected and the thioredoxin lowering activity of PX-12 in plasma samples is being assessed. One patient with refractory colon cancer has experienced a minor response and completed 14 cycles of therapy starting with 9 mg/m²/day and escalating to 36 mg/m²/day. To date, nine of patients have had stable disease, receiving between 4 and 9 cycles of therapy. Escalation and accrual is ongoing. (Supported by ProlX Pharmaceuticals)
Cell cycle and death control: Long live Forkhead

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The members of the FOXO family of Forkhead transcription factors, FKHR (FOXO1), FKHR-L1 (FOXO3a) and AFX (FOXO4) are regulated by the phosphoinositide 3-kinase (PI3K)/protein kinase B (PKB/c-Akt) pathway. Direct phosphorylation by PKB results in cytoplasmic retention and inactivation of the FOXO transcription factors. Consequently the expression of FOXO-regulated genes, involved in control of the cell cycle, cell death, metabolism and oxidative stress, is inhibited. Reactive oxygen species are required for cell proliferation but can also induce apoptosis. In proliferating cells this paradox is solved by the activation of protein kinase B (PKB; also known as c-Akt), which protects cells from apoptosis. By contrast, it is unknown how quiescent cells that lack PKB activity are protected against cell death induced by reactive oxygen species. Here we show that the PKB-regulated Forkhead transcription factor FKHR-L1/FOXO3a protects quiescent cells from oxidative stress by directly increasing their quantities of manganese superoxide dismutase (MnSOD) messenger RNA and protein. This increase in protection from reactive oxygen species antagonizes apoptosis caused by glucose deprivation. In quiescent cells that lack the protective mechanism of PKB-mediated signalling an alternative mechanism is induced as a consequence of PKB inactivity. This mechanism entails the activation of Forkhead transcription factors, the transcriptional activation of MnSOD and the subsequent reduction of reactive oxygen species. Increased resistance to oxidative stress is associated with longevity. The model of Forkhead involvement in regulating longevity stems from genetic analysis in Caenorhabditis elegans, and we conclude that this model also extends to mammalian systems.
The Role of Secondary DNA Structures in Silencing Transcription

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The role of secondary DNA structures in control of gene expression has long been debated. In this presentation I provide direct evidence for a G-quadruplex in a promoter region and its targeting with a small molecule to repress c-MYC transcription. The nuclease hypersensitivity element IIII upstream of the P1 promoter of c-MYC controls 85–90% of the transcriptional activation of this gene. We have demonstrated that the purine-rich strand of the DNA in this region can form two different intramolecular G-quadruplex structures, only one of which appears to be biologically relevant. This biologically relevant structure is the kinetically favored chair-form G-quadruplex, which when mutated with a single G to A transition is destabilized, resulting in a 3-fold increase in basal transcriptional activity of the c-MYC promoter. The cationic porphyrin TMPyP4, which has been shown to stabilize this G-quadruplex structure, is able to further suppress cMYC transcriptional activation. These results provide compelling evidence that a specific G-quadruplex structure formed in the c-MYC promoter region functions as a transcriptional repressor element. Furthermore, we establish the principle that c-MYC transcription can be controlled by ligand-mediated G-quadruplex stabilization. The formation of similar G-quadruplexes in other promoters of growth regulatory genes (unpublished results), such as PDGF-A, c-myb, and RET, suggest that this will be a more general phenomenon in genes associated with growth and proliferation. The sequestration of the active form of the promoter as a G-quadruplex rather than in a nucleosome may have advantages for a rapid response required for genes involved in proliferation and may have been an ancient mechanism for controlling gene expression.
Hypoxia inducible factor-1α (HIF-1α) as a novel target for cancer drug development: PX-478 an antitumor inhibitor of HIF-1α

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Hypoxic cancer cells are found in all solid tumors in regions where tumor growth outstrips new blood vessel formation. Hypoxic cancer cells are resistant to chemotherapy and radiation and are a major reason for the failure of current cancer therapy. New knowledge of the cellular biology of the response to hypoxia provides novel ways of attacking hypoxic cancer cells and exploiting their unique biology for selective therapy. HIF-1 is a transcriptional activator that mediates the response of cells to hypoxia. Genes activated by HIF-1 allow the cancer cell to adapt its energy metabolism to the hostile anaerobic state, to be resistant to programmed cell death (apoptosis) and to metastasize to new less hypoxic environments. HIF-1 also induces the production of a family of cytokines, including vascular endothelial growth factor (VEGF), that promote the formation of new tumor capillary blood vessels from pre-existing blood vessels (angiogenesis). HIF-1 is a heterodimer consisting of a HIF-1α subunit that undergoes rapid ubiquitination and proteasomal breakdown in air but is stabilized under hypoxic conditions, and an oxygen-insensitive HIF-1β (ARNT) subunit. HIF-1α is absent in normal tissue but increased in many human tumors. Inhibiting HIF offers a new way attacking hypoxic tumor cells and of selectively preventing the cell survival, angiogenic and metastatic effects of hypoxia in tumors.

PX-478 is a novel small molecule inhibitor of the hypoxia-induced increase in HIF-1α in a variety of cancer cells with an IC₅₀ of 5 -10 µM. PX-478 appears to act by increasing the degradation of HIF-1α in hypoxia. PX-478 also inhibits hypoxia induced HIF transactivating activity and VEGF formation by the cells. PX-478 administered ip at 60 to 120 mg/kg daily for 5 days to scid mice with large established (up to 0.8 g) human tumor xenografts (MCF-7 breast cancer, PC-3 prostate cancer, HT-29 colon cancer and OvCar-3 ovarian cancer) gives dose dependent tumor regressions, in some cases of greater than 90%, and growth delays up to 60 days. The log10 cell kill by PX-478 is typically 1.0 to 2.0. The extent of growth inhibition by PX-478 appears to positively correlate with tumor HIF-1α levels measured by immunohistochemistry. Caki-1 renal cancer which has constitutively elevated HIF-1α is also sensitive to growth inhibition by PX-478 (regression 44%, log10 cell kill = 0.9). Peak plasma levels of PX-478 after an ip dose of 150 mg/kg are 500 ?g/ml and the t1/2 63 min. A single ip dose of PX-478 125 mg/kg administered to mice with HT-29 colon tumors causes a rapid 60 % decrease in tumor HIF-1α within 1 hr and a 82 % decrease in plasma VEGF. Both HIF-1α and VEGF have returned to pretreatment levels by 8 hr. Thus, PX-478 is the first of a novel class of HIF-1α inhibitors and its excellent antitumor activity occurs with inhibition of the tumor target HIF-1α target and plasma VEGF.
Choline kinase is a new target for cancer therapy: when, why and how ChoK inhibitors work as specific antitumor drugs

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Choline Kinase (ChoK), the enzyme responsible for the generation of phosphorylcholine (PCho) from its precursor choline, is the first enzyme in the Kennedy pathway that renders Phosphatidylcholine (PC) as its final product. Since PC is the most abundant component of the plasma membrane, this pathway has an essential structural function. In addition, generation of PCho from ChoK activity is a critical event in growth factors-induced mitogenesis in murine fibroblasts. Furthermore, several oncogenes such as ras, src or mos, induce an increase of both ChoK activity and intracellular levels of PCho. Keeping with the role of ChoK and PCho in malignant transformation, ChoK is up-regulated in human mammary carcinomas with a high incidence as well as in lung, colorectal and prostate tumors. The observation of enhanced ChoK activity in consonance with its mitogenic properties constitutes the basis of the design of a new antitumoral strategy focused on specifically inhibiting this enzyme. Thus, ChoK inhibitors have been generated with proved antiproliferative activity against oncogene-transformed cells and human tumoral cells. MN58b, a selective inhibitor of ChoK, is rather specific to this enzyme with no effect on a variety of oncogene-activated signalling pathways involved in the regulation of cell proliferation. MN58b does not affect MAPKs, PI3K, and other enzymes involved in the regulation of phospholipid metabolism such as phospholipases C, D, and A2, CTP:phosphocholine cytidylyltransferase (CT), or diacylglycerol choline-phosphotransferase (CPT). Consistent with this specificity, ectopic expression of ChoK resulted in resistance to its inhibitor. Finally, non-transformed cells were able to resume cell proliferation after removal of the drug, while transformed cells were irreversibly affected. These results indicate that inhibition of ChoK is a rather specific strategy for the cytotoxic treatment of transformed cells.

We have also investigated the clinical implications of ChoK activity in the carcinogenic process in human tumors. Breast cancer is still one of the most important tumors among women in industrialised countries. As a consequence of its relevance, it has been the target of many clinical trials resulting in a reduction of mortality of women with this malignancy. However, improvement in both understanding the molecular events associated to the disease and the development of new additional treatments is still an important goal to be achieved. We have investigated the relevance of ChoK in human breast cancer and found that the expression of this enzyme is increased in human mammary adenocarcinomas with high incidence (38.5%). Furthermore, this activation is associated with clinical parameters indicators of greater malignancy such as high histologic tumour grade and ER-negative tumours. We will report evidence for a role of ChoK in normal human mammary epithelial cells proliferation and in breast tumour progression, and the therapeutic effect of ChoK inhibitors in human...
breast cancer cells. The potential use of this antitumoral strategy based on ChoK inhibition as a novel approach for breast cancer patients will be discussed. Finally, a possible mechanism underlying the antiproliferative effect of ChoK inhibition will be discussed.

References:
Cancer represents a disease prototype that is connected to defects in the cellular signal transduction network that controls proliferation, motility, survival and recognition by the immune system. The spectrum of genetic alterations identified in cancer cells includes mutations in various genes leading to structural and functional dysfunctions in signal transmission and definition as well as over- or underexpression of positive or negative signal generating or regulating proteins respectively. For the past years we have investigated various aspects of signaling systems in tumor cells in order to identify critical switchpoints in the pathophysiological process that results in malignancy. These efforts aim at the selective blockage of abnormal, disease-promoting signaling mechanisms rather than the eradication of all growing cells in the body as in the case of currently used chemotherapeutics and began with the cloning of EGF receptor cDNA and the related receptor HER2/neu. Recently the work that began in 1983 yielded the first specific oncogene-based therapeutic “Herceptin” for the treatment of mammary carcinoma. Analogous “target-driven drug development“ efforts have led to the identification of a germ line mutation in the FGF receptor 4-gene which in the case of breast cancer predisposes the carrier for a more aggressive progression of the disease, which emphasizes the potential value of the FGFR4 as target for the development of anti-metastatic therapeutics. Moreover, through the identification of a crosstalk mechanism between G protein-coupled receptors and members of the EGFR family, new cancer relevant targets have been identified that are upstream of the EGFR and include membrane-standing metalloproteases. In addition to the investigation of genetic alterations involved in cancer development and metastasis we have characterized Flk-1/VEGFR2 as a critical signaling element in tumor angiogenesis which represents the basis for the development of novel anti-angiogenic therapies for a broad spectrum of cancers.
Abstracts-posters

In alphabetical order of presenting author
Effects of Lycopene on Proliferation of Human Breast Cancer T47D cells and its Tamoxifen Resistant subtype

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Breast cancer is one of the commonest malignancies of women worldwide, particularly in the western countries. Despite a great deal of efforts to combat the disease, its therapy fails due to different reasons that amongst them drug resistance is an important factor. In our studies we decided to look at the effects of Lycopene, a natural and strong antioxidant from tomato, on proliferation of human breast cancer T47D cells and its Tamoxifen (TAM) resistant subtype (TAMR-6). We isolated the TAMR-6 cells, that are resistant to TAM (1 x 10⁻⁶ M), from parent T47D cells by gradual exposure of parent cells to increasing concentrations of TAM (1 x 10⁻⁹ – 1 x 10⁻⁵ M). The purity and potency of Lycopene that was extracted from fresh tomato verified by mass spectrometry and biological activity against standard Lycopene (Sigma, UK), respectively. Parent and TAMR-6 cells were seeded in 24-well culture plates and exposed to different concentrations of extracted Lycopene (1 x 10⁻⁸ – 1 x 10⁻⁵ M) alone or in combination with TAM (1 x 10⁻⁶ M) for different time points up to 6 days. The ANOVA and student’s T-test performed on the obtained mean of data for control (RPMI 1640 culture media) and different treatments indicated the dose dependent effect of Lycopene on decreasing proliferation of both cell types. Lycopene at 5 x 10⁻⁶ M had almost the same effect on cell proliferation as TAM at 1 x 10⁻⁶ M. The effect of Lycopene on both cell types was almost the same except for 1 x 10⁻⁵ M which was significantly (P< 0.001) more on parent T47D than TAMR-6 cells. The combination of Lycopene and TAM showed a synergistic effect on further decrease in cell proliferation that was significantly (P<0.001) different from control or either compound alone. In conclusion, our results indicated that Lycopene is a good candidate to be looked at for possible anti breast cancer applications as preventive or therapeutic herbal medicine.

Keywords: Breast cancer, herbal medicine, Lycopene.
Serum pyrrolidon carboxypeptidase activity in N-methyl nitrosourea induced rat breast cancer

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Pyrrolidon carboxypeptidase (Pcp) (E.C. 3.4.19.3) is an omega peptidase widely distributed in animal fluids and tissues, which hydrolyses N-terminal pyroglutamic residues from biologically active peptides such as gonadotropin releasing hormone (GnRH). Previous results obtained by us showed a decrease in human breast cancer Pcp activity, suggesting that this enzyme activity or its putative substrates may play a major role in breast cancer pathogenesis. The aim of the present work is to analyse serum Pcp activity in N-methyl-nitrosourea (NMU) induced rat mammary tumours using pyroglutamyl-ß-naphthylamide as substrate. Serum Pcp activity was significantly lower in NMU-treated rats than in controls. Moreover, multiple regression analysis showed a significant correlation between Pcp activity and the number and size of tumours and the body weight of the animals. Due to NMU-induced carcinomas are mainly estrogen-dependent, the decrease observed in Pcp activity may reflects an increase in circulating levels of GnRH, which lead to increase on gonadal steroid hormones production, responsible, at least in part, of the initiation and promotion of the disease.
Inositol Pentakisphosphate Promotes Apoptosis through the PI 3-K/Akt Pathway

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Phosphoinositide 3-kinase (PI 3-K) is implicated in a wide array of biological and pathophysiological responses, including tumorigenesis, invasion and metastasis\(^{1}\). Therefore, PI 3-K is an attractive therapeutic target, and specific inhibitors of the kinase may prove useful in cancer therapy. We have shown that micromolar concentrations of specific inositol phosphates inhibit growth of human cancer cell lines containing a constitutively active PI 3-K\(^{2}\). These effects appeared to be specifically related to pleckstrin homology (PH) domains, lipid-binding modules involved in tethering proteins to specific membrane compartments\(^{3}\). We propose that specific inositol phosphates, namely the soluble head groups of the phosphoinositides, have the potential to antagonize the activation of PI 3-K pathways by competing with the binding of PtdIns(3,4,5)P\(_3\) to PH domains\(^{4}\).

Here we investigate the effect of inositol phosphates on the PI 3-K/Akt signaling pathway and show that Ins(1,3,4,5,6)P\(_5\) is able to block the Akt/PKB signaling pathway, by inhibiting both its serine phosphorylation and its kinase activity. As a consequence of the inhibition of the Akt/PKB survival pathway, Ins(1,3,4,5,6)P\(_5\) is able to induce apoptosis in ovarian, lung and breast cancer cells. Overexpression of constitutively active Akt protects SKBR-3 cells from Ins(1,3,4,5,6)P\(_5\)-induced apoptosis. Our findings suggest that inhibition of the PI 3-K/Akt pathway by Ins(1,3,4,5,6)P\(_5\) enhances the proapoptotic effect of cisplatin and etoposide in ovarian and lung cancer cells respectively. These results support a role for Ins(1,3,4,5,6)P\(_5\) as a specific inhibitor of the PI 3-K/Akt signaling pathway, that may sensitize cancer cells to the action of commonly used anticancer drugs. Our subsequent goal will be to develop more selective and potent inhibitors of Akt PH domain binding to phosphoinositides starting from the Ins(1,3,4,5,6)P\(_5\) structure.

The present study has been designed to provide new drugs that act by mimicking known protein structure specificities at the level of their membrane localization through protein-phosphoinositide interactions. The PI 3-K signaling cascade may play a critical role in tumorigenesis, invasion and metastasis. The identification of new functional inhibitors of PI 3-K pathway would provide new tools for the treatment of tumors whose progression is driven by PI 3-K activation or PTEN gene alterations. Since the PTEN gene is deleted or mutated in a wide variety of human cancers the results of this study may have wide clinical implications.

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Purine based inhibitors of cyclin-dependent kinases


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As the first CDK specific inhibitor olomoucine was identified by our group, blocking specifically CDK1, CDK2 and CDK5 kinases. Its structure modifications led to the discovery of roscovitine, novel substance with enhanced inhibitory activity, increased selectivity and antimitotic activity, then purvalanol A, and recently olomoucine II, which are effective in submicromolar concentration. The correlation between CDK1/2 inhibition and cytotoxicity of purine derivatives suggests that the CDK inhibition is at least partly responsible for the antiproliferative activity of the compounds.

Up to now the advancement of olomoucine has been based mainly on modifications of substituents at positions 2, 6 and 9, respectively. In our current effort to enhance the affinity of purine inhibitors to CDKs, we rearrange the purine heteroatoms and introduce another side chains, respectively. The inhibitor-CDK mutual interactions are verified by molecular modelling.
Prodigiosin, a new proapoptotic drug: DNA interaction and topoisomerase inhibition

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The cytotoxic properties of the prodigiosin-group natural products has determined by the National Cancer Institute (NCI)\(^1\), and more specifically, prodigiosin, a red pigment produced by Serratia marcescens, facilitates cell death by apoptosis and exhibit selective activity against haematopoietic\(^2\), gastric\(^3\) and colon cancer cell lines\(^4\) and in B-cell chronic lymphocytic leukaemia from twenty patients\(^5\), with no marked toxicity in nonmalignant cell lines.

During a study of prodigiosin internalisation we observed that this drug reached the nucleus in a very short time. This prompted us to approach a sequence of investigative steps. First, to better characterise the mode of prodigiosin interaction with DNA. Second, to explore the potential topoisomerase inhibition properties of prodigiosin. Finally, to evaluate DNA damage induced by prodigiosin in cultured cells.

We examined the mechanism of action of prodigiosin, focusing on its interaction with DNA and its ability to inhibit topoisomerase I. We also evaluated the DNA damage induced by prodigiosin in Jurkat cell line. We demonstrated that prodigiosin can be internalised by mammalian cells. Prodigiosin is observed in both cytoplasmic membranous systems and the nucleus. The prodigiosin-DNA interaction involved prodigiosin-intercalation, which abolished the activity of the topoisomerase I enzyme, and DNA cleavage. The nicking activity of prodigiosin was associated with the pH (6.8 better than 7.4) and with the Cu\(^{2+}\) ion concentration. Finally, visualisation of dose-dependent chromosomal DNA fragmentation corroborated the prodigiosin-DNA damage in Jurkat cells.

These results indicate that DNA is a therapeutic target for prodigiosin and could explain the apoptotic mechanism of action induced by this antineoplastic drug, especially when it is used in the presence of Cu\(^{2+}\) and under acid conditions.

ACKNOWLEDGEMENTS
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Chemical Genetic Approaches to Selective Inhibitors of Histone Deacetylases

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Chemical genetics utilizes small organic molecules instead of genetic mutations to perturb the functions of proteins rapidly and conditionally, thus allowing biological processes to be explored through phenotypic and protein-binding assays. Concomitant with the development of such assays, there is an urgent need for the development of synthetic routes toward structurally complex and functionally diverse compounds having the potential to modulate biological processes. The small molecule approach allows for the identification of proteins that can serve as targets for therapeutic intervention as well as the discovery of powerful chemical tools to probe biological pathways. In recent years, there has been an increased interest in histone deacetylase (HDAC) inhibitors as potential anticancer agents for the treatment of solid and hematological malignancies. HDACs modulate gene expression through the deacetylation of the N-acetyl lysine residues of histone proteins and other transcriptional regulators. To date, three classes of mammalian HDACs have been identified: class I and class II HDACs are zinc hydrolases; class III HDACs are NAD-dependent hydrolases. The development of isoform-specific small molecule inhibitors of HDACs should facilitate the identification of the role of individual HDACs on gene expression and other biological processes. A structural rationale for HDAC inhibition is suggested by the X-ray crystal structure of trichostatin A (TSA, a known inhibitor) bound to HDAC-like protein (HDLP), an HDAC ortholog from the thermophilic bacterium *Aquifex aeolicus*. The high degree of sequence similarity of the active site of HDLP to those of the class I and class II HDACs inspired a short, stereoselective, diversity-oriented synthetic route toward a library of ca. 11,000 TSA analogs. These analogs possess metal-binding functionality and a cap region that are connected by a 5-6 atom hydrocarbon linker, thus acting as substrate mimics of the lysine side chain. Notably, a vector of molecular descriptors for each compound in the library was calculated for comparison to a reference set of known nonspecific HDAC inhibitors.

The HDAC inhibitor library is constructed using the split-pool method on polystyrene macrobeads, where each chemical step is encoded with unique molecular tags. Each macrobead yields sufficient compound post-cleavage (ca. 0.1 mg per bead) to generate individual compound stock solutions ready for both phenotypic and protein-binding assays. The design scheme is also amenable to the synthesis of homodimeric compounds. Existing small molecule microarray technology and HDAC inhibition assays will be used to uncover small molecules that distinguish between class I and class II HDACs. The discovery of these compounds can motivate powerful biological tools and core scaffolds for potential therapeutics.

(vii) M. S. Finnin et al., Nature (1999) 401, 188.
Inhibition of Choline Kinase as a specific cytotoxic strategy in H-Ras transformed cells

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Cancer research is in the need of selective drugs that can specifically interfere with those signalling pathways affected during the carcinogenic process. Identification of new potential molecular targets is one of the key events in the design of new strategies. Once identified, generation of specific molecules to regulate their function is the most important goal. We have previously demonstrated the relevance of dysregulation of choline kinase in oncogene-driven cell transformation. Here we provide evidence that inhibitors to choline kinase are rather specific to this enzyme with no effect on a variety of oncogene-activated signalling pathways involved in the regulation of cell proliferation. Choline kinase inhibitors did not affect MAPKs, PI3K, and other enzymes involved in the regulation of phospholipid metabolism such as phospholipases C and D, phospholipase A2 or Citydilyl-transferase. Also, the incorporation of either choline or glycerol into relevant phospholipids such as phosphatidylcholine and lyso-phosphatidylcholine, phosphatidyl-serine or sphingomyeline was not affected. Consistent with this specificity, overexpression of choline kinase resulted in resistance to the drug. Finally, non-transformed cells were able to resume cell proliferation after removal of the choline kinase inhibitor, while transformed cells were irreversibly affected. These results indicate that inhibition of choline kinase is a rather specific strategy for the cytotoxic treatment of transformed cells.
Organisers and Invited Speakers’ Portfolio

A compilation of short biographies of organisers and speakers in accordance with the order of the scientific programme
Amancio Carnero, Ph.D.  
Head, Assay Development Group  
Experimental Therapeutics Programme  
Centro Nacional de Investigaciones Oncológicas, Madrid, Spain

Amancio Carnero was awarded with his Ph.D. in Molecular Biology at the Universidad Autónoma de Madrid, Spain, in 1994, for work on ras signal transduction pathway at the Instituto de Investigaciones Biomédicas (CSIC).

He moved to the Cold Spring Harbor Laboratory, USA, where he worked on strategies of gene isolation based on function in mammalian cells in D. Beach’s Group. Armed with a long term Postdoctoral Fellowship granted by the European Molecular Biology Organization (EMBO), the period 1997-2000 was also spent under the supervision D. Beach, as Senior Research Fellow at the Institute of Child Health, London, UK. His research interests focused on the cell cycle, replicative senescence and cellular immortalisation.

Carnero was to spend one further year in London based at the Wolfson Institute for Biomedical Research, as Senior Lecturer, before returning to Spain in 2001 to assume his current position as Head, the Assay Development Group, Centro Nacional de Investigaciones Oncológicas, Madrid.

Current research focuses on the identification of new genes involved in cancer, the identification and validation of new targets for anticancer drug discovery, the design of assays for compound screening and finally, the design and generation of tools for preclinical validations of these drugs.
Born in Obninsk, Russia, Ruben Abagyan received his Ph.D. from the Moscow State University in 1984 for his work on molecular modeling and diffraction theory under the direction of N.G. Esipova and V.G. Tumanyan. He continued to work independently at the Engelhardt Institute of Molecular Biology, Moscow, on the molecular modelling theory, DNA structure, and sequence analysis.

In 1989 he joined J. Marcial’s Protein Engineering Laboratory at the University of Liege in Belgium. In 1990 he moved to the European Molecular Biology Laboratory (EMBL) in Heidelberg, Germany where he became Staff Scientist at Argos’ Group.

In 1994 he moved to New York University where he set up a Computational Biology Laboratory at the Skirball Institute of Biomolecular Medicine directed by L. Philipson and became Associate Professor of Biochemistry (at the NYU Medical School) and Mathematics (at the Courant Institute of Mathematics).

It was in 1999 when Ruben Abagyan settled as Professor at the Scripps Research Institute in La Jolla, California. From 1999 to 2001 he also served as Director of Computational Biology at the Genomics Institute of the Novartis Research Foundation.

His main focus since 1985 has been to formulate and develop a new method for macromolecular simulations to make them more predictive, efficient and easily applicable to a variety of modeling tasks, including folding, homology modelling, loop predictions and protein design, protein docking and small ligand docking and virtual screening. In 1991 he applied the first version of the Internal Coordinates Mechanism program (ICM) to molecular structure prediction. He founded the company Molsoft to continue the development of this program.

In collaboration with A. Mazur, he was the first to describe the equations of motion for macromolecules in the internal coordinates. In 1993, with R. Wierenga, he successfully applied the ICM energy optimisation method to targeted redesign of a part of protein backbone.
Tom Blundell has been a Sir William Dunn Professor of Biochemistry at the University of Cambridge since 1995. His research interests surround the molecular architecture of living organisms. He has worked on enzymes involved in hypertension and AIDS and on vertebrate lens proteins involved in cataract. His research now focuses on growth factors, receptor activation and signal transduction, important in cancer and other diseases. He was appointed in 1976 as Professor of Crystallography at Birkbeck College, the University of London, and in 1989 as Honorary Director, Imperial Cancer Research Fund Unit of Structural Molecular Biology.

His research has been recognised by the Alcon Award for Vision Research, the Gold Medal of Institute of Biotechnology, the Krebs Medal of the Federation of European Biochemical Societies. He is a Member of Academia Europaea, a Fellow of both the Royal Society and the Academy of Medical Sciences. He has Honorary Fellowships at Linacre and Brasenose Colleges, Oxford University, and a Professorial Fellowship at Sidney Sussex, Cambridge, in addition to Honorary Doctorates from thirteen universities.

Tom Blundell has played an active role in national science policy. In the 1980s he was a Member of the advisory group to the Prime Minister (ACOST). He has been a Member of the Royal Society Council and is currently a Member of the Advisory Committee of the Parliamentary Office for Science and Technology, POST. He has had a long involvement in research councils, culminating in his appointment as Director General, Agricultural and Food Research Council (1991-1994) and Chief Executive, Biotechnology and Biological Sciences Research Council, BBSRC (1994-1996).

Tom Blundell has been Chairman of the Royal Commission on Environmental Pollution since 1998, producing a report on “Energy, the Changing Climate” in 2000 and on “Environmental Planning” in March 2002.

He is currently a non-executive Director and Chairman of the Scientific Advisory Board of Celltech. In 1999 he co-founded Astex Technology, a company dedicated to the discovery of new medicines, based at the Cambridge Science Park, UK.
Peter M. Fischer, Ph.D.
Head, Discovery Research
Cyclacel Limited, Dundee, Scotland, UK

Peter M. Fischer was born in Switzerland, where he received his early education. He subsequently studied in Australia and received his Ph.D. in 1989 from Deakin University, Geelong (Melbourne), Victoria, Australia, working with M. E.H. Howden on peptide toxins. His career has taken him to positions in academia, as well as in the biotechnology and pharmaceutical industries, where he has worked on peptidomimetic and traditional medicinal chemistry projects related to drug discovery. Previous to his current appointment he headed a Medicinal Chemistry Group at Nycomed, Oslo, Norway, working on drug design projects in the areas of haematopoiesis, as well as thrombosis and haemostasis. For the last five years he has been with the cancer research company Cyclacel, in Dundee, Scotland, for whom he established structure-based design and medicinal chemistry capabilities. At present he leads the multi-disciplinary drug discovery research efforts. His research currently focuses on cell cycle-related drug discovery targets, including cyclin-dependent kinases and other protein kinases.

Fischer has published numerous research papers and review articles on peptide and medicinal chemistry, as well as authoring many patents. He is a member of several professional societies, including the American Chemical Society (ACS), the European and American Peptide Societies, the American Association for Cancer Research (AACR), and the Royal Society of Chemistry, of which he is a Fellow Member.
Paul Workman is Director of the Cancer Research UK’s Centre for Cancer Therapeutics at The Institute for Cancer Research, Sutton, UK. He is also the Harrap Professor of Pharmacology and Therapeutics at the University of London and a Cancer Research UK Life Fellow. In addition, he holds the posts of Visiting Professor in Pharmacology at the University of Manchester and External Professor of Cancer Pharmacology at the University of Leeds, where he completed his Ph.D. (1977). Previous appointments include Cancer Research Section Head at Zeneca (now AstraZeneca) Pharmaceuticals (1993-1997), Director of Laboratory Research and Cancer Research UK, Professor of Experimental Cancer Therapy at the Department of Medical Oncology, Beatson Laboratories, University of Glasgow (1990-1993), Sabbatical Visitor at Stanford University, California (1989) and Staff Member of the Medical Research Council Clinical Oncology Unit, MRC Centre, Cambridge University (1976-1990). Workman was awarded the European School of Oncology Award for Excellence in Oncology Research (1985), and is also a Cancer Research UK Life Fellow (1991) and has been elected a Fellow of the Institute of Biology (1997) and a Fellow of the Academy of Medical Sciences. He is considered an international reference in cancer pharmacology and drug development. He has over 30 years experience in all phases of drug development and has been involved in taking several new drugs into the clinic, including the epidermal growth factor receptor inhibitor Iressa (now approved in Japan), the Hsp90 molecular chaperone inhibitor 17AAG, the cyclin-dependent kinase inhibitor CYC202 and the hypoxia detection agent SR4554. His particular research interests have focused on the discovery, development and mechanism of action of new cancer drugs, particularly those aimed at inhibiting signal transduction pathways used by growth factors and oncogenes in cancer cells and agents designed to detect and eradicate solid tumours based on their low oxygen content. He has published over 350 research articles in cancer pharmacology and drug development. Workman has acted as a Consultant or Scientific Advisory Board Member for a large range of pharmaceutical and biotechnology companies and is a Scientific Founder and Board Director of Chroma Therapeutics and also a Scientific Founder of Piramed.
Mariano Barbacid was born in Madrid, Spain. He got his Ph.D. degree in Biochemistry at the Universidad Complutense of Madrid in 1974. From 1974-1978 Barbacid was a postdoctoral fellow in the National Cancer Institute in Bethesda, Maryland. In 1978 he formed his own group to work on the molecular biology of sarcoma viruses. At that time, he also explored the possibility that human tumours may carry activated oncogenes similar to those found in transforming retroviruses. This work led to the identification and cloning of the first human oncogene in 1981 and its subsequent identification the following year as a mutated allele of the H-ras protooncogene.

In 1984, Barbacid moved to the Basic Research Programme – NCI, FCRF, in Frederick Maryland as Head of the Developmental Oncology Section and in 1988, Barbacid joined the Bristol Myers-Squibb Pharmaceutical Research Institute in Princeton, New Jersey where he became Vice President, Oncology Drug Discovery in 1995. During this time, Barbacid was responsible for implementing a target-based drug discovery programme that focused on farnesyl transferase and cell cycle inhibitors, some of which are currently in clinical trials. As part of his basic research efforts, it is worth mentioning the identification of the Trk family of tyrosine protein kinases as the neurotrophin receptors.

His work has been recognised by several awards, among others, the Distinguished Young Scientist Award (Maryland Academy of Sciences, 1983), the King Juan Carlos I Award (Spain, 1984), the Rhodes Award of the American Association of Cancer Research (USA, 1986), the Steiner Prize (Switzerland, 1988) and the Ipsen Prize (France, 1994). In 1998, Barbacid returned to Spain to create and subsequently direct the Centro Nacional de Investigaciones Oncológicas (CNIO). When fully operational (2004-2006), the CNIO will have a staff of about 500 scientists dedicated to basic and applied cancer research. The Barbacid lab is concentrating on the study of the role of cell cycle regulators in vivo and on the design of new animal models for cancer by using gene-targeting technologies.

Barbacid has published more than 160 original papers in international scientific journals and more than 50 invited reviews and book chapters. He serves in numerous Scientific Advisory Committees and belongs to the Editorial Board of more than fifteen international scientific journals.

He has been an EMBO Member since 1996.
Jaume Piulats, Ph.D.
Director of Research, Laboratorio de Bioinvestigación (LBI), Merck Farma y Química, S.A.
Barcelona, Spain

Jaume Piulats obtained his Ph.D. at the School of Pharmacy of the University of Barcelona. He is a specialist in Pharmacology from the School of Medicine of the University of Barcelona and in immunology at the Autonomous University of Barcelona. His Postdoctoral training in Immunology was carried out at the Universities of London and Cambridge (UK). He is currently an Associate Professor in Immunology at the University of Barcelona and Director of Research of the Laboratorio de Bioinvestigación (LBI) of Merck Farma y Química, S.A., Barcelona, Spain.

During the last eighteen years, the Laboratorio de Bioinvestigación has focused on reaching new targets for cancer therapy in three main areas: immunotherapy (monoclonal antibodies and cancer vaccines), modulation of cell cycle machinery and regulation of tumour angiogenesis. Piulats’ lab is the core reference for angiogenesis studies within the Merck Group.

Piulats’ team has developed monoclonal antibodies for therapy and a ganglioside (GD3) based vaccine for melanoma treatment. They are also studying the potential role of E2F transcription factor as target for cancer therapy and, finally, research focuses on the search for new targets and agents for anti-angiogenic therapy. His research activity has been consolidated through a wide spectrum of external cooperations with institutions such as the Salk Institute, Scripps Institute, Wistar Institute, Sloan-Kettering Cancer Center (US), MRC (UK), University of Lille (France) and many Spanish Research Centres (Universities of Barcelona and Valencia, CSIC, IRO, ICO, IVO, etc).
In 1994, Scott Lowe was awarded with his Ph.D. in Biology from the Massachusetts Institute of Technology (MIT), for work at the Center for Cancer Research, MIT, Cambridge, USA. His studies established that defects in apoptosis can produce treatment-resistant tumours and suggested that p53 status was a key determinant in apoptosis and tumour response to therapy.

He moved to the Cold Spring Harbor Laboratory in 1995 where he was initially appointed as Fellow. From 1996 Lowe’s career witnessed a series of promotions, leading to his current positions. Aside from his Research Appointment, Lowe currently holds two Academic Appointments at the State University of New York (SUNY), Stony Brook.

His research mainly focuses on the role of apoptosis and senescence in cancer therapy. His laboratory has identified factors that act downstream of p53, and is assembling these components into a tumour suppressor network. Moreover, his laboratory has studied human tumours and animal models to confirm the relevance of this working model for tumour development and cancer therapy in vivo.

Lowe serves on several Editorial Boards and he is also author of patents related to cancer therapy.
David Beach, Ph.D., FRS
President, Genetica, Inc.
Boston, USA

David Beach obtained his Ph.D. at the University of Miami studying the development of the retina in Xenopus. As a Post-doctoral Fellow at the University of Sussex, UK, he characterised early replicating DNA in the slime mould and went on to isolate the origin of replication in the budding yeast. Alongside P. Nurse he developed the techniques for genetic transformation of the fission yeast and showed the functional equivalence of the budding yeast cdc28 and fission yeast cdc2 genes.

After moving to Cold Spring Harbor Laboratories in 1982, Beach initially elaborated the molecular structure of the complex fission yeast mating-type locus with A. Klar. Thereafter, he used genetic techniques to uncover interactions between cyclin genes. That led, in collaboration with J. Rudermann and G. Draetta, to show that cyclins physically associate to create a key cell cycle regulating kinase with multiple cellular substrates. In subsequent studies Beach discovered human cyclin D, analysis that led to the discovery of p21, p15, p16, CDC25, SKP1 and SKP2. p16, discovered by M. Serrano in his lab, was shown to be a specific inhibitor of cyclin D derived kinases and is a gene associated with familial melanoma.

He was also senior author of numerous papers reporting the complex regulation of cell cycle proteins. In collaboration with S. Lowe and colleagues, Beach studied cellular senescence and its abrogation in tumour cells. In particular, the well-characterised oncogene ras was shown to trigger premature senescence in otherwise genetically normal cells.

Their studies led to the development of a set of techniques for improved genetic dissection of mammalian cells. In collaboration with G. Hannon, the MaRX retroviral vectors were developed. After moving to the University College London, Beach undertook an in-depth analysis of cellular senescence genes, using MaRX, RNAi and microarray analysis.

To summarise, David Beach has devoted his scientific career to understanding the mechanisms that regulate cell multiplication in eukaryotes, and currently is centering efforts at Genetica Inc., where he serves as President.

Beach has been a Howard Hughes Medical Institute Investigator and also the Hugh and Catherine Stevenson Professor of Cancer Biology. He has received the Young Investigator Award of the American Association of Microbiology, the Eli Lilly Research Award, the Raymond Bourgine Cancer Research Award and along with C. Sherr, the Bristol Myers Squibb Award. He is a Fellow of the Royal Society of London.
Andrei Gudkov began his research career in the former Soviet Union, where he obtained his Ph.D. in 1982 and Doctor of Sciences degree in 1988, for work at the National Cancer Research Center in Moscow focused on studies of endogenous retroviruses and mechanisms of genomic instability and multidrug resistance of cancer cells.

After moving to the United States in 1990, he worked in I. Roninson’s Laboratory at the University of Illinois in Chicago, specifically on the development of a genetic suppressor element (GSE) approach, a gene discovery methodology that is based on functional gene knockout GSEs isolated from retroviral libraries of randomly fragmented cDNAs.

After establishing his independent laboratory in 1993, Gudkov continued exploring the GSE approach that resulted in the identification of several genes mediating drug sensitivity and transformation. In 1996, a series of p53-modulating GSEs were isolated in his lab, which marked the beginning of his long-term interest in p53. This interest was extended towards the analysis of the role of p53 in development, function and stress response of normal mammalian tissues. Based on the results of genetic analysis of p53 response in vivo, he defined p53 as a major determinant of cancer treatment side effects and suggested considering this protein as a target for therapeutic suppression. The first p53 inhibitor pifithrin-alpha was isolated in 1999 in Gudkov’s lab by screening a diverse chemical library in a cell-based readout system. Pifithrin was shown capable of protecting animals from lethal doses of radiation, the result that validated p53 inhibition as an approach to reduce cancer treatment side effects.

In 2001, he moved his laboratory from Chicago to Cleveland, Ohio, to the Lerner Research Institute at The Cleveland Clinic Foundation, where he became Chairman of the Department of Molecular Biology. Here he continued developing his gene and drug discovery programs, extending them to new cancer areas and drug targets, benefiting from being housed in one of the leading clinics within the USA. His lab has recently developed a new gene discovery methodology - a selection-subtraction approach (SSA) - that greatly strengthened the power of functional screenings of expression libraries, including the possibility of a direct negative selection that has never been possible before. SSA is being used to identify new prospective drug targets for cancer.
Reuven Agami received his Ph.D. in 1999 from The Weizmann Institute of Science in Israel where he worked on DNA damage responses and apoptosis induced through c-Abl and p73. He completed his Postdoctoral training with a long-term European Molecular Biology Organization (EMBO) Fellowship, under the supervision of R. Bernards, at the Division of Molecular Carcinogenesis, the Netherlands Cancer Institute, Amsterdam, working on the connection between DNA damage and rapid cell cycle responses mediated through cyclin D1 destruction.

Since 2001, Agami has been appointed as Staff Member at the Division of Tumor Biology at the Netherlands Cancer Institute, where his laboratory focuses on the stable suppression of gene expression in mammalian cells through short interfering RNAs, and its potential use for therapy, and also on the study of cellular DNA damage responses.

In 2001, he received the Netherlands Cancer Institute Award, and was Elected Fellow of the Center of Biomedical Genetics, The Netherlands.
Bin-Bing Zhou obtained his Ph.D. degree in Molecular and Cell Biology in December 1993 from the University of California-Berkeley, USA, under the supervision of H. K. Schachman on biophysical characterizations of the allosteric enzyme aspartate transcarbamoylase. He then completed his postdoctoral studies in Cell Biology at M. W. Kirschner’s group, Harvard Medical School, Boston, USA, during which time he was working on cytoskeleton and cell cycle control.

From 1998 until mid-2002, Zhou worked for GlaxoSmithKline, in the Department of Oncology Research, where he was Group Leader for multiple cancer drug discovery efforts, and was instrumental in setting up anti-checkpoint and anti-mitotic efforts there.

Late last year, he has joined Incyte Genomics to head the Molecular Oncology group.

Specific contribution made by Zhou can be found in the field of DNA damage checkpoints and cancer therapeutics. His expertise is called upon by several Editorial Boards, adjunct faculty positions, and he is also a member of key American Scientific Associations.
Craig B. Thompson, M.D.
Scientific Director, Abramson Family Cancer Research Insitute
The University of Pennsylvania Cancer Center
Philadelphia, USA

Craig B. Thompson was awarded with his M.D. from the University of Pennsylvania in 1977, and served his internship and residency in Internal Medicine at Harvard’s Peter Bent Brigham Hospital. In 1979 he moved to Boston’s University Hospital as Senior Resident.

Thompson was later a physician at the National Naval Medical Center in Bethesda, from 1981 to 1983 and an Assistant Professor of Medicine at the Uniformed Services University of the Health Sciences, also in Bethesda, from 1982 to 1987. Also, between 1983 and 1985, he was a Fellow in Hematology and Oncology at the Fred Hutchinson Cancer Research Center at the University of Washington.

From 1987 to 1993, Thompson was a member of the Department of Medicine at the University of Michigan, and a Howard Hughes Institute Associate Investigator. In 1993, he became the Director of the Knapp Center at the University of Chicago and a Howard Hughes Medical Institute Investigator. Thompson assumed his current position at the Abramson Institute as Scientific Director in 1999.

He studies the genes that regulate apoptosis and investigates their application in treating cancer. Thompson’s laboratory has pioneered the study of the Bcl-2 family of oncogenes, or cancer-causing genes, and their role in regulating cell survival. Based on this research, future treatments could be designed to block the ability of cancer cells to survive, and thus limit tumor size and prevent the cancer from spreading. His lab is interested in bettering understanding of how apoptosis is regulated and also in generating preventive treatments for individuals predisposed to cancer.

With a list of over 250 publications, Thompson serves as Associate Editor of several of the highest impact factor journals. He is a recipient of numerous prestigious awards and honours, most recently for example, he delivered the Jean and Jerome Pearlstein Lecture, at Dana-Farber Cancer Center, Harvard University.
Laurent Meijer was trained at the University of Lille where he obtained his Ph.D. in 1978 under the supervision of M. Durchon. This was followed by Post-doctoral studies at the Hopkins Marine Station, the Stanford University Marine Laboratory, in D. Epel’s Laboratory. His work focused on the changes in protein phosphorylation in Urechis oocytes fertilisation and cell cycle. He then obtained a research position at the CNRS and joined P. Guerrier’s Group at the “Station Biologique de Roscoff”, where he investigated the role of protein phosphorylation during the G2/M transition in the starfish oocyte. In 1985, he joined E. Krebs’ and B. Shapiro’s group at the University of Washington, Seattle, USA. There, he extensively characterised the so-called M-phase specific Histone H1 kinase, a kinase activated in all cells as they enter the M phase of the cell division cycle.

In 1988, his group, collaborating with D. Beach at Cold Spring Harbor, identified the catalytic subunit of this kinase as CDC2, now known as CDK1. He identified the associated regulatory subunit as cyclin B, and in 1990, demonstrated that the CDK1/cyclin B complex was activated by subtle changes in phosphorylation of both subunits. As this fundamental research was carried out, Meijer became interested in using these essential cell cycle regulators as molecular targets for the identification of new anti-mitotic agents of potential therapeutic interest. In 1991, the CDK1 screening method was described, followed by the cdc25 screening method in 1992.

Meijer’s group also participated in the race through the identification, characterisation and optimisation of a few families of chemical inhibitors of cyclin-dependent kinases: olomoucine, rosco-vitine, purvalanol, paullones, indirubins, hymenialdisine, aloisines, etc. These inhibitors have generated interest in various fields of cell biology and in the medical area, due to their potential applications against cancer, neurodegenerative disorders, viral infections, unicellular parasites, etc. They have reached the pre-clinical and clinical stages of development as therapeutic agents against cancer and glomerulonephritis.

His group focuses on basic aspects of cell cycle regulation, with a strong interest in kinase inhibitors. Besides cyclin-dependent kinases, he is studying glycogen synthase kinase 3 (GSK3), that belongs to a group of kinases with multiple implications in cellular functions. He is currently Visiting Professor at P. Greengard’s Laboratory at the Rockefeller University, New York, studying brain protein kinases.
After undergraduate studies at Oxford University, Nick Tonks conducted his graduate research in P. Cohen’s Laboratory at the University of Dundee, UK, and was awarded a Ph.D. in 1985. From 1985-88 he performed postdoctoral research in the laboratory of one of the pioneers of the field of protein phosphorylation, E. Fischer, at the Department of Biochemistry of the University of Washington (UW) in Seattle. In 1988 he accepted a junior faculty position at the UW and continued to work with Fischer until 1990. While in Seattle, Nick Tonks purified for the first time an enzyme termed a protein tyrosine phosphatase (PTP). With his collaborators he sequenced the protein, termed PTP1B, demonstrated homology with CD45, a cell surface marker on lymphocytes, and determined that CD45 possessed intrinsic PTP activity. These observations laid the foundation for the study of PTPs as regulators of signal transduction and established the existence of receptor-linked PTPs with the potential to trigger signalling responses through ligand-controlled dephosphorylation of tyrosyl residues in proteins. Although the importance of tyrosyl phosphorylation in the control of signal transduction was appreciated, this work led to a shift in emphasis to encompass the concept that tyrosine phosphorylation is reversible and subject to regulation in vivo at the level of both protein phosphorylation and dephosphorylation. It is now appreciated that the PTP family of enzymes play critical and diverse physiological roles from cell adhesion to the control of proliferation. Furthermore, the PTPs are now the subject of strategies for the development of novel therapeutics for various human diseases including, diabetes, obesity, inflammation and cancer.

In 1990, Tonks moved to Cold Spring Harbor Laboratory and has been Professor since 1994. His current research interests remain focused on the PTPs and his lab continues to make important contributions in this area. In 1995 he founded CEPTYR Inc, a biotechnology company dedicated to the development of PTP-based therapeutics.

His achievements have been recognised by several awards including a Pew Scholarship in the Biomedical Sciences from 1991-95 awarded by the Pew Charitable Trusts, The 1993 Colworth Medal, awarded annually by the British Biochemical Society to an outstanding British Biochemist under the age of 35 and a MERIT Award from the National Institutes of Health awarded in 2001. He is also a Fellow of the Royal Society, the UK National Academy of Sciences.
Boudewijn Burgering received his Ph.D. degree in Medicine from the University of Leiden in 1991. In 1992 he moved to the University of Utrecht where he was appointed as a Post-doctoral Fellow at H. Bos’ Laboratory (Physiological Chemistry), and then later as an Associate Professor when he initiated his research group.

His research focuses on signal transduction by the insulin receptor and other receptor tyrosine kinases. This work emerged from his earlier studies concerning the role of the small GTPase Ras in tumorigenesis and led to the seminal findings that insulin activates Ras and that Ras is involved in the regulation of MAPkinase. Later, his interest shifted to the role of the lipid kinase PI3K in cellular responses to insulin and growth factor treatment. This led to the discovery of the protein kinase B (PKB, also known as c-Akt) and the Forkhead transcription factors of the FOXO class as important mediators of insulin function. Current interest is in the role of these FOXO factors in determining the cellular redox status.

In 2002 he was elected as Member of the European Molecular Biology Organization (EMBO) and Member of the EARSC.
Laurence H. Hurley was awarded with his Ph.D. in Medicinal Chemistry in 1970 from Purdue University, USA. After several academic appointments, he became Professor at the University of Kentucky in 1979. He joined the Drug Dynamics Institute at the College of Pharmacy, The University of Texas at Austin in 1981, as Professor of Medicinal Chemistry. In 1995 Hurley accepted the position as Director of Chemistry at the Institute for Drug Development, Cancer Therapy Research Center, San Antonio, Texas, an appointment that he held until 2000. He then relocated to The University of Arizona in Tucson, where he holds the Howard J. Schaeffer Endowed Chair in Pharmaceutical Sciences in the College of Pharmacy.

Hurley’s current research interests are in the design and development of antitumour agents. Over the last twenty years, work from his laboratory has led to elucidation of the structures of the drug–receptor complexes for seven different groups of compounds that are potentially useful in the treatment of cancer. In cooperation with the pharmaceutical industry, several drugs developed with the aid of these studies have been evaluated in phase I and II clinical trials. Most recently, his research has centred on secondary DNA structures, particularly G-quadruplexes as gene targets for drug design and the identification of a novel mechanism of action for Et 743, a drug presently in phase II clinical trials.

Laurence Hurley is a Fellow of the American Association for the Advancement of Science. He is Founder and Scientific Director of Cyternex, a biotech company in San Diego. As recognition for his work, he has received the 1988 George Hitchings Award in Innovative Methods in Drug Design, the 1989 Volwiler Research Achievement Award from the American Association of College of Pharmacy. He is also the recipient of the 1992 APhA Research Achievement Award in Medicinal Chemistry and the 1994 ACS Medicinal Chemistry Award. In 1996 he was awarded a D.Sc. degree from Bath University, from where he also received his B.Pharm. in 1967.
Garth Powis received his D.Phil. in Biochemistry and Physiology from Oxford University, U.K. He was a Lecturer in Pharmacology at the University of Glasgow, Scotland before moving to the USA working at Yale University, and then as a Consultant in Oncology and Professor of Pharmacology at Mayo Clinic, Rochester, Minnesota. In 1992 he moved to the Arizona Cancer Center as Director of Basic Research and Professor of Pathology, Pharmacology, Molecular and Cell Biology.

The focus of his work is the identification and validation of novel cancer drug targets and translational studies of molecularly targeted cancer drugs. His recent work focuses on redox control of cancer cell growth and death, and cell survival pathways principally the phosphatidylinositol-3-kinase /PTEN/ Akt pathway. Agents have been developed as potential cancer drugs to inhibit various points on these pathways one of which is already in the clinic as a thioredoxin inhibitor with other agents as HIF-1α inhibitor, phosphatidylinositol-3-kinase inhibitor and Akt inhibitor are in various stages of preclinical development.

Powis is on the Editorial Board of numerous journals and the author of more than 280 papers, 3 books and has 6 patents in the area of cancer drug discovery and development.
Juan Carlos Lacal, Ph.D.
Professor of Research and Group Leader
Instituto de Investigaciones Biomédicas, CSIC, Madrid, Spain

Juan Carlos Lacal received his Ph.D. in 1982 from the Universidad Autónoma de Madrid, Spain. From 1983-88 he served as an EMBO Postdoctoral Fellow, then as a Postdoctoral Fellow of the Fogarty International Center (NIH) and then as Visiting Associate in the Laboratory of Cellular and Molecular Biology, National Cancer Institute (Bethesda Maryland, USA). In 1989 he joined the Spanish Research Council as Investigator at the Instituto de Investigaciones Biomédicas, Madrid. From 1991-94 he was elected as Secretary General of the Spanish Association for Cancer Research/ASEICA, then as Vice-President (1995-1996), and President (1997-1998). He served as Member of the Executive Committee of the Spanish Federation of Cancer Societies/FESEO (1991-1994 and 1997-1998), as Member of the Executive Committee of the European Association for Cancer Research/EACR (1996-2000) and as Member of the Council of the Federation of European Cancer Societies/FECS (1997-1999).

His research interest has focused on the identification of signal transduction pathways altered after oncogenic transformation, towards the aim of identifying new molecular targets and designing novel antitumour strategies. His major contribution has been made in the field of small GTPases within the Ras superfamily, and in particular the Ras and Rho families. Importantly his work was pioneering in identifying enzymes involved in phospholipid metabolism activated by Ras oncogenes such as phospholipase D and choline kinase, which have been the basis for the design and synthesis of new antitumour drugs. Furthermore, his work on the oncogenic, apoptotic, and metastatic properties of Rho GTPases has been pioneering in this field. At last, the identification of specific transcription factors activated by the family of Rho GTPases, has been of great relevance in defining the biological properties of Rho GTPases. He has published 130 articles in specialised journals and books.

He has been the recipient of several awards for his research accomplishments, such as the Fundación Salud 2000 Research Award in 1992, and the Fundación Dr. Antonio Esteve Research Award in 1999.
Alex Ullrich was awarded with his Ph.D. in Molecular Genetics from the University of Heidelberg, Germany in 1975. From 1975-78, he worked at the University of California, Department of Biochemistry and Biophysics, San Francisco where he cloned the preproinsulin cDNA, that led to the development of the first genetechology based therapeutic protein product by Genentech, Inc. This company, based in South San Francisco, was key to Ullrich’s career from 1979-1988, where he assumed positions as Senior Scientist and Staff Scientist respectively. His research there spanned the elucidation of the primary structure of the precursor proteins for EGF, NGF and other growth factors, and membrane and nuclear receptor. One of these, the growth factor receptor HER2/neu, with a major role in mammary and ovarian carcinoma progression, was used for the first target-specific anticancer gene therapy by this company, that is available to patients since 1998.

1988 witnessed his appointment to his actual current position: Director, the Department of Molecular Biology, Max-Planck Insitut für Biochemie. His major research achievements in this period are related to the fields of angiogenesis and anti-angiogenesis therapy with the identification of Flk-1/VEGF-R as a target for the development of antiangionic drugs.

Ullrich has developed numerous patents related to cancer therapy, he is Member to many Scientific Advisory Boards, spanning the globe, not to mention several key Editorial duties for a variety of scientific publications. He has received numerous awards and honours - most recently, the King Faisal International Prize for Medicine, Saudi Arabia (2003).
Organisers, Speakers, and Participants List
## Organisers and Invited Speakers List

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### 2003 CNIO CCC’s. Targeted Search for Anti-Cancer Drugs

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## Participants List

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As a non-profit organisation, we would like to thank the support from our CNIO Cancer Conferences (CCC’s) sponsors. 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 surrounding forthcoming exhibition and sponsorship opportunities, please contact: Amanda Wren, Tel. +34 91 2246985, Fax. +34 91 2246981, Email: awren@cnio.es
Notes
2003 CNIO CCC’s. Targeted Search for Anti-Cancer Drugs
2003 CNIO CCC’s. Targeted Search for Anti-Cancer Drugs
Forthcoming CNIO activities
**FORTHCOMING 2003 CNIO ACTIVITIES**

**CNIO Cancer Conferences (CCC)**

**Small GTPases in Human Carcinogenesis**  
*Organisers:* Juan C Lacal, Channing Der, Shuh Narumiya  
*Dates:* June 16-18, 2003

**Apoptosis and Cancer**  
*Organisers:* Gabriel Nuñez, Marisol Soengas, Scott Lowe  
*Dates:* December 1-3, 2003

**CNIO Meetings**

**2003 DNA Arrays**  
*Organisers:* Ana Dopazo, Joaquín Dopazo, Orlando Domínguez, Ignacio Casal  
*Dates:* May 9, 2003

**2003 Tissue Microarrays**  
*Organisers:* Miguel A. Piris, Ignacio Casal, Lydia Sánchez  
*Dates:* October 20, 2003

**Other Activities**

**The Breast Cancer Linkage Consortium (BCLC) and the International Collaborative Group on Familial Breast and Ovarian Cancer (ICG-FBOC): 14th General Meeting**  
*Organisers:* Javier Benítez, Peter Devilee, David Goldgar, Diana Eccles  
*Dates:* June 2-4, 2003

**First CNIO-NCI Joint Meeting: Advances on Cancer Research**  
*Organisers:* Miguel Ángel Piris, José Palacios, María J. Merino  
*Dates:* June 26-27, 2003 (main sponsor: DAKO)

**Curso de Cancer de Mama (European School of Oncology Course in Spanish)**  
*Organisers:* José Palacios, Miguel Martin  
*Dates:* October 16-17, 2003

**Workshop on SNPs Analysis, Tools and Applications (Founded by the European Science Foundation)**  
*Organisers:* Javier Benítez, Mercedes Robledo, Joaquín Dopazo  
*Dates:* November 28-29, 2003