Instituto Juan March
de Estudios e Investigaciones

104 CENTRO DE REUNIONES
INTERNACIONALES SOBRE BIOLOGÍA

1999
Annual Report

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Headquarters of the Fundación Juan March
(Home of the Centre for International Meetings on Biology)

There are two sides to every question, exactly opposite to each other.

Protagoras, quoted by **Diogenes Laertius** in "*Lives and Opinions of Eminent Philosophers*"

INSTITUTO JUAN MARCH DE ESTUDIOS E INVESTIGACIONES

CENTRE FOR INTERNATIONAL MEETINGS ON BIOLOGY

1999 ANNUAL REPORT

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FOREWORD

This publication covers the activities of the Centre for International Meetings on Biology during the year 1999. All of them were, in due time, broadly announced by means of brochures, posters, advertisements in scientific journals and other periodicals.

The core of the Centre's work during 1999 was the organization of thirteen workshops, dealing with very different biological topics. An introduction to each of these meetings is presented here, followed by a list of invited speakers and participants selected from among the applications received. In total, 266 speakers were invited to the meetings during this year, and 393 participants were chosen from among the 552 applications received.

13 booklets were published on these meetings, including the abstracts of the contributions presented by the participating scientists. About 400 copies of each booklet were distributed to research groups and laboratories working on problems relating to the subject of each meeting.

A new series of the Juan March Lectures on Biology was organized in 1999, a tradition in the Centre since 1982. Information on these lectures is also included in the following pages. Another four sessions open to the general public were held to coincide with meetings mentioned above.

A short notice is given on reviews published during 1999 in scientific journals, regarding meetings organized by the Centre.

The schedule of meetings to take place in 2000 is also offered in this report.

Instituto Juan March de Estudios e Investigaciones

THE CENTRE FOR INTERNATIONAL MEETINGS ON BIOLOGY

The Centre for International Meetings on Biology endeavours actively and systematically to promote close cooperation and interaction among Spanish and foreign scientists working in the field of Biology. This scientific field is understood in the widest sense, and emphasis is given to advanced lines of research.

The Centre's activities stem from the Plan for International Meetings on Biology, initiated by the **Fundación Juan March** in January 1989 and ending in December 1991. A wide range of meetings and scientific activities were organized under this Plan. The Fundación Juan March, in addition to its well-known support of the fine arts and culture in general, has devoted particular attention to the biological sciences since its creation in 1955 by the Spanish financier Juan March Ordinas.

The Centre for International Meetings on Biology was established in January 1992 within the **Instituto Juan March de Estudios e Investigaciones**, a private foundation created in October 1986 and recognized by the Spanish Ministry of Education and Culture. This foundation complements the work of the Fundación Juan March, as an entity specializing in scientific activities. The Board of Trustees of the Instituto comprises: Juan March (Chairman), Carlos March (Deputy Chairman), Leonor March, Alfredo Lafita, Antonio Rodríguez Robles, Pablo Vallbona, Enrique Piñel and Jaime Prohens (Secretary). José Luis Yuste is Managing Director of the Institute.

The Centre for International Meetings on Biology is located at Calle Castelló 77, Madrid.

SCIENTIFIC COUNCIL AND MANAGEMENT OF THE CENTRE

The Scientific Council of the Centre comprises the following members:

Miguel Beato
Institut für Molekularbiologie und
Tumorforschung. Marburg (Germany)

José A. Campos-Ortega
Institut für Entwicklungsbiologie. Köln (Germany)

Gregory Gasic
Neuron Editorial Office. Cambridge (USA)

César Milstein
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Centro de Biología Molecular. CSIC - Universidad
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Ramón Serrano
Instituto de Biología Molecular y Celular de Plantas.
CSIC – Universidad Politécnica de Valencia (Spain)

The Scientific Council determines the priorities for the Centre's activities. It may put forward initiatives to be carried out in collaboration with Spanish or foreign laboratories. It will also consider proposals of meetings submitted to the Centre by Spanish or foreign scientists, selecting and approving those it feels deserve support.

In general terms, the Scientific Council advises the Centre for International Meetings on Biology on any scientific subject or issue falling within the scope of the Centre's activities.

The Director of the Centre is **Andrés González**.

1999 Meetings Schedule

CENTRE FOR INTERNATIONAL MEETINGS ON BIOLOGY
1999 MEETINGS SCHEDULE

Date	Meeting Subject	Organizers
8-10 February	**Eukaryotic Antibiotic Peptides**	**J.A. Hoffmann.** Institute de Biologie Moleculaire et Cellulaire. Strasbourg. **F. García-Olmedo.** E.T.S. de Ingenieros Agrónomos. Madrid. **L. Rivas.** Centro de Investigaciones Biológicas. Madrid.
8-10 March	**Regulation of Protein Synthesis in Eukaryotes**	**M.W. Hentze.** EMBL. Heidelberg. **N. Sonenberg.** McGill University. Montreal. **C. de Haro.** Centro de Biología Molecular "Severo Ochoa". Madrid.
22-24 March	**Cell Cycle Regulation and Cytoskeleton in Plants**	**N.-H. Chua.** The Rockefeller University. New York. **C. Gutiérrez.** Centro de Biología Molecular "Severo Ochoa". Madrid.
12-14 April	**Mechanisms of Homologous Recombination and Genetic Rearrangements**	**J.C. Alonso.** Centro Nacional de Biotecnología. Madrid. **J. Casadesús.** Facultad de Biología. Universidad de Sevilla. **S.C. Kowalczykowski.** University of California. Davis. **S.C. West.** Imperial Cancer Research Fund. Herts.
26-28 April	**Neutrophil Development and Function**	**F. Mollinedo.** Facultad de Medicina. Universidad de Valladolid. **L.A. Boxer.** University of Michigan. Ann Arbor.
10-12 May	**Molecular Clocks**	**P. Sassone-Corsi.** IGBMC. Université Louis Pasteur. Strasbourg. **J.R. Naranjo.** Instituto Cajal. Madrid.
24-26 May	**Molecular Nature of the Gastrula Organizing Center: 75 years after Spemann and Mangold**	**E.M. De Robertis.** HHMI. University of California. Los Angeles. **J. Aréchaga.** Universidad del País Vasco. Leioa.
7- 9 June	**Telomeres and Telomerase: Cancer, Aging and Genetic Instability**	**M.A. Blasco.** Centro Nacional de Biotecnología. Madrid.
4- 6 October	**Specificity in Ras and Rho-mediated Signalling Events**	**J.L. Bos.** Universiteit Utrecht. **J.C. Lacal.** Instituto de Investigaciones Biomédicas. Madrid. **A. Hall.** University College London.
18-20 October	**The Interface Between Transcription and DNA Repair, Recombination and Chromatin Remodelling**	**A. Aguilera.** Facultad de Biología. Universidad de Sevilla. **J.H.J. Hoeijmakers.** Erasmus University. Rotterdam.
11-13 November	**Dynamics of the Plant Extracellular Matrix**	**K. Roberts.** John Innes Centre. Norwich. **P. Vera.** Instituto de Biología Molecular y Celular de Plantas. Valencia.
20-22 November	**Helicases as Molecular Motors in Nucleic Acid Strand Separation**	**E. Lanka.** Max-Planck-Institut für Molekulare Genetik. Berlin. **J.M. Carazo.** Centro Nacional de Biotecnología. Madrid.
13-15 December	**The Neural Mechanisms of Addiction**	**R.C. Malenka.** University of California. San Francisco. **E.J. Nestler.** Yale University School of Medicine. New Haven. **F. Rodríguez de Fonseca.** Facultad de Psicología. Universidad Complutense de Madrid.

Eukaryotic Antibiotic Peptides

Organized by
J. A. Hoffmann, F. García-Olmedo and L. Rivas

(8-10 February)

Until few years ago, antibiotic peptides in eukaryotes were considered as an evolutionary relic, especially when compared with the powerful and complex immune response present in higher mammals. In 1972 the first experimental evidence of plant peptides (thionins) active against plant pathogens was published, but it was not until the end of the 70's that this field started an exponential growth on a broad variety of different sceneries. Nowadays, several antibiotic peptides and their analogues are in advanced clinical trials, and some human pathological disorders have been related to their absence or lack of function.

Eukaryotic antibiotic peptides contribute both to the control of local bacterial flora and as a first-line barrier against pathogen invasion, as demonstrated in insect mutants deficient in some antibiotic peptides or in transgenic plants overexpressing particular antibiotic peptides. In higher vertebrates, their importance in health is less known; as aforementioned, the strength of antigen-specific immunity, as well as the simultaneous presence of other components of innate immunity, hamper the definition of the roles of specific peptides, and although some transgenic mice expressing defensins have been recently developed, overexpression and knock-out experiments with mice are lagging behind those with plants. The protective role of antibiotic peptides in human health is emphasized by the recently found correlation between recurrent bacterial lung infections in cystic fibrosis and lack of activity of local antibacterial peptides because of the high salinity in the alveolar fluid, due to the genetic default in chloride transport.

Besides constitutive expression of some antibiotic peptides in mammals, infectious and inflammatory processes can modulate their expression, mediated by LPS, IL-1, IL-2, or TNF-α. Furthermore, an evolutionary convergence in some of their signal transduction pathways, involving members of the Rel/NF-κB family occurs among plants, insects, amphibia and mammals.

To date, more than 400 sequences of both natural and derived antibiotic peptides have been described; despite large differences in size and amino acid sequences, most of the antibiotic peptides share a strong cationic character and adopt an amphipatic structure in their interaction with model or biological membranes. Their mechanism of action is often based on permeabilization of the plasma membrane of the pathogen with dissipation of the ionic gradients across the membrane with subsequent bioenergetic collapse of the organism; the permeabilization is brought about by disruption of phospholipid bilayer rather than by interaction with chiral receptors or channels; hence discrimination between self and non-self is mostly based on membrane lipid composition, as prokaryotes are devoid of sterols and possess a higher percentage of anionic phospholipids when compared with eukaryotes. This mechanism is double-edged; the design of peptides with higher membrane affinity risks a substantial loss of specificity and production of self-damage; by contrast and in support of a pharmaceutical application, resistance against membrane-active antibiotic peptides prompted by continuous culture at sub-lethal concentrations has not been reported yet, even when some pathogens possess a natural resistance to some of these peptides. To reach the inner membrane of Gram negative bacteria, antibiotic peptides need first to disrupt the outer membrane by interaction with lipopolysaccharide. In most cases, this leads to inhibition of the events triggered by LPS, such as endotoxic shock, hence the peptides can also work as antiendotoxemic agents. In many cases, chemical synthesis of these peptides or their analogues is easily afforded, giving access to studies of structure-activity relationships, aiming at the design of better and more active analogues.

In summary, the workshop has succeeded in updating our knowledge on this fascinating field, where many different biological disciplines, as well as organisms from very diverging origins, converge to provide answers and to create great expectations for future pure and applied research.

J. A. Hoffmann, F. García-Olmedo and L. Rivas

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Regulation of Protein Synthesis in Eukaryotes

Organized by
M. W. Hentze, N. Sonenberg and C. de Haro

(8-10 March)

An important part of the control of gene expression in eukaryotic cells occurs at the post-transcriptional level. Translation regulation allows the cell to quickly respond to environmental changes. Post-transcriptional regulation of gene expression appears to play a major and often underestimated role in the efficient production of specific proteins by the eukaryotic cells.

The mechanisms of mRNA translation have been a topic of research for many years. The realization that protein synthesis is regulated by biological signals or programs has emerged much more recently. These mechanisms are now beginning to be understood.

This Workshop on "Regulation of Protein Synthesis in Eukaryotes" brought together experts and leaders in this emerging field. The presentations focussed on the responsible translation factors, regulatory RNA sequences, regulatory proteins and a broad scope of biological systems including those from developmental biology, growth control, cell differentiation and viruses. Many new discoveries were presented and discussed for the first time in public. Not only invited papers but also the communications presented as posters in this Workshop were important contributions to grasp the current state and the scenario for future developments on the field.

True to the typical character of the Juan March Workshops, the discussions were intensive, thorough and stimulating. On behalf of ourselves and of all participants we would like to thank the Juan March Foundation for making possible and very pleasant this Workshop.

New ideas and a sense of excitement were what many participants took home in addition to much new information.

Matthias Hentze, Nahum Sonenberg and César de Haro

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Cell Cycle Regulation and Cytoskeleton in Plants

Organized by
N.-H. Chua and C. Gutiérrez

(22-24 March)

Progression through the cell cycle stages occurs as a temporally coordinated series of events that involve the concerted action of both positive and negative acting effectors. In addition, the cellular decision to enter and/or exit the cell cycle is the physiological response to a series of external and internal stimuli.

The basic eukaryotic cell cycle is well exemplified by the situation found in yeasts, unicellular eukaryotic organisms with a powerful genetics, where many details of the molecular framework regulating the transits through the G1/S and the G2/M boundaries are known.

Multicellularity requires the superimposition of a number of extra control pathways derived from the need to integrate signals as well as from the specific developmental patterns. In animals, cell cycle regulators also participate actively in the maintenance of certain differentiated status. Initial studies revealed that basic cell cycle regulators, such as some cyclins or cyclin-dependent kinases (CDKs), are strikingly conserved in animal and plant cells. However, plants have unique growth and developmental properties and display a specific response to environmental signals and plant hormones. Therefore, it is likely that the regulatory pathways controlling cell cycle progression and the exit from active proliferation to differentiation in response to growth signals are different from those operating in animal cells.

In the last 3-4 years, an enormous advance in this field has occurred regarding several aspects of the plant cell cycle in terms of the identification of new genes encoding cell cycle regulators, such as homologs of the human retinoblastoma tumor suppressor protein, novel CDKs, or specific CDK inhibitors. Now, we are facing an extremely exciting future since very recent results are providing us with hints which clearly point to novel roles of cell cycle regulators in plant development and body architecture. Which is the molecular basis for the significant plasticity of plant cells? Why plant cells are extremely refractary to neoplastic transformation? How cell cycle regulators contribute to the maintenance of a particular differentiated state and how they contribute to shape the plant body? These are just a few examples.

Another level of complexity, unique to plants, comes from the immobility of cells within the plant body. The importance of the plane of division and the significant role of cell expansion in the generation of plant organs make necessary a strict coordination between cell cycle control and the cellular components which provide the framework for cell division, i. e., the cytoskeleton. Cytoskeletons are likely involved in the establishment and maintenance of patterns during plant cell morphogenesis. Cytokinesis in plant cells is distinct from that in animal cells in several important aspects. The plane of cell division is presaged by a preprophase band which is comprised of microtubules. At the zone marked by the preprophase band, the phragmoplast, a complex array of microtubules, microfilaments and secretory vesicles, grows through a centrifugal process giving rise finally to the cell plate that divides the two daughter cells. Because cell differentation in plants is often presaged by asymmetric cell divisions, the placement of the preprophase band must be regulated by signalling events. Actin, tubulins and dynamin-like proteins contribute to develop a functional cell plate which is the basis for plant cytokinesis.

In summary, several interesting aspects related to the topics outlined above have been the subject of this workshop. A significant amount of novel results and unpublished data were presented. As expected from their potential impact in the field, they triggered active discussions throughout the meeting. Based on the directions where the plant cell cycle field is moving, we look forward to very exciting developments in the near future.

Crisanto Gutiérrez and Nam-Hai Chua

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Mechanisms of Homologous Recombination and Genetic Rearrangements

Organized by
J. C. Alonso, J. Casadesús, S. C. Kowalczykowski and S. C. West

(12-14 April)

Cells are constantly facing the challenge of repairing alterations in their genetic material. DNA damage occurs under normal physiological conditions and can be exacerbated by environmental factors. Cells have evolved several distinct mechanisms of DNA repair and DNA-damage tolerance, which help to maintain the structural and informational fidelity of their genome. A large body of evidence supports the idea that, when those mechanisms fail, accumulated genetic changes lead to a number of diseases, including the development of neoplasia.

The process of genetic recombination continues to shape and reshape the genomes of all organisms, thereby enhancing the variation generated by mutations and increasing the polymorphism of natural populations. Recombination is also used widely as a tool, for both genetic analysis of biological processes and engineering of new gene constructs and transgenic organisms. A knowledge of recombination is therefore crucial to many areas of basic biology, biotechnology and medicine. The analysis of molecular reactions involved in recombination has witnessed significant developments in the last decade. A large number of recombination genes and proteins have been identified; in a number of cases, their activities have been associated with specific reactions.

At the cellular level, failure to repair damaged DNA is associated with sensitivity to radiation, increased mutation rates, DNA and chromosomal aberrations, defects in cell division, and reduced viability. At the clinical level, human diseases with known or suspected defects in repair show a range of symptoms, including a high incidence of malignancy, photosensitivity, immunodeficiency, neurological disorders, growth retardation, premature aging, and death. The contributions presented in the workshop highlighted the major role of homologous recombination in the maintenance of the structural and informational fidelity of DNA.

The participants at the workshop represented an international group of prominent investigators with diverse interests, backgrounds, research strategies and viewpoints. This diversity, together with the precise focus of the meeting, permitted a critical evaluation of recent progress in the field. On the other hand, the breadth and depth of the topics presented, the small size of the meeting, the presence of young motivated participants, and the intimate and stimulating atmosphere of the Juan March Institute combined to produce a highly informative workshop with lively and inspiring discussions.

J. C. Alonso, J. Casadesús, S. C. Kowalczykowski and S. C. West

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Neutrophil Development and Function

Organized by
F. Mollinedo and L. A. Boxer

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Neutrophils are the most abundant leukocytes in blood and constitute the first line of defense against infectious diseases. These short-lived non-mitotic cells are generated at impressive numbers in the bone marrow as the result of a highly controlled process of myelopoiesis. Despite the huge number of neutrophils made daily in the bone marrow, many of them do not meet microorganisms but undergo apoptosis. Mature neutrophils are fully equipped with an arsenal of harmful agents stored in granules ready to be used to destroy phagocytosed microorganisms. The neutrophil availability for combating infections is regulated at different levels: proliferation and maturation of precursor cells in bone marrow, regulation of programmed cell death, migration through the endothelial cell barrier, activation of bactericidal systems. Failure to accomplish some neutrophil functions can lead to severe clinical disorders such as Chronic Granulomatous Disease (CGD) and Leukocyte Adhesion Deficiency (LAD). The genetic processes regulating neutrophil development in the bone marrow as well as the modulation of adhesion, diapedesis, migration, exocytosis, respiratory burst and apoptosis as well as the pathophysiological processes leading to clinical disorders were the focus of the workshop. This meeting dealt with novel trends in neutrophil structure, function and development. Thus, this workshop covered molecular events regulating the whole life-span of the neutrophil, including how it is generated, activated and removed after undergoing an apoptotic process. All of these processes are finely regulated and we are now starting to understand them at the molecular level.

Myeloid cell production is regulated by a complex interacting network of cytokines that modulate proliferation, differentiation, apoptosis and mobilization of hematopoietic stem and progenitor cells. Chemokines, an emerging family of cytokines, are being increasingly implicated in the production, mobilization and activation of neutrophils, showing a high redundancy in their actions. One of the major decisions leading to neutrophil generation is made by stem cells committed to the myeloid lineage, when granule protein coding genes are turned on to provide the synthesis of the granule constituents that will endow the neutrophil with its battery of microbicidal proteins. CCAAT enhancer binding proteins (C/EBPs), in particular C/EBPα, play a central role in neutrophil development and synthesis of neutrophil granule proteins. CCAAT displacement protein, a negative regulator, must be down-regulated to allow expression of certain granule proteins. However, regulation of granule protein biosynthesis is individually controlled, and differences in timing of granule protein synthesis during maturation of neutrophil precursors results in formation of granule subsets with different protein content. Mature neutrophils are very short-lived leukocytes that die by spontaneous apoptosis. This process is not simply a way of getting rid of unused neutrophils or of cells after having performed their task, but may control the number of neutrophils available in combating infections.

Experiments of nature (LAD) as well as man-designed studies have demonstrated that neutrophil extravasation depend on its ability to adhere, via integrins, to the endothelium. Integrins behave both as docking and signaling molecules that mediate leukocyte adhesion as well as actin-cytoskeletal rearrangement and regulation of several neutrophil functional responses, such as migration, degranulation and respiratory burst. Neutrophils tend to adhere and transmigrate at endothelial cell borders, where P-selectin acts as a target for neutrophil migration. When ICAM-1 is highly expressed on activated endothelial cells, neutrophil adhesion proceeds via direct β_2-integrin-ICAM-1 recognition. Studies using bone marrow-derived neutrophils from $fgr^{-/-}/hck^{-/-}$-knockout mice indicate that Fgr and Hck are not required for myeloid cell development, but are critical in controlling integrin-mediated responses such as generation of superoxide anion, adhesion, migration and degranulation. Adherence

and motility are non-static processes and firm-loose cycles would allow cell movement. In order to explain the observed cycles in movement and respiratory burst, a novel mechanism was proposed involving metabolic clocks in neutrophils with cycles in the free concentration of essential metabolites (ATP and NADPH) which regulate downstream activities. Chemoattractants promote changes in neutrophil shape with the formation of a uropod at the rear of the cell, which can attract other neutrophils during neutrophil transmigration. Also, the most abundant neutrophil proteins MRP8/14, which together account for 45% of the cytosolic neutrophil protein were suggested to play a role, once released from cells, in neutrophil migration and adhesion.

Phagocytosis and secretion, two critical functions of neutrophils, involve docking and fusion of intracellular vesicles with the plasma membrane modulated by specific proteins. To compensate loss of cell surface during phagocytosis, cells generate from the trans-Golgi network vesicles to fuse with the nascent phagosomes. Different intracellular granules are mobilized independently during neutrophil exocytosis, and granule constituents, secreted or translocated into the cell surface upon cell activation, affect neutrophil adhesion and diapedesis. The identification of SNARE proteins in human neutrophils as well as their differential subcellular localization (plasma membrane *vs* granule) and functional assays, suggest a role of these proteins in both neutrophil phagocytosis and secretion.

The power of gene transfection was shown to be useful in dissecting the role of Fcγ receptors and their signaling. Phospholipase D seems to play an important role in phagocytosis signaling. Phospholipase D activation triggers a signaling cascade, involving Raf-1 and ERK-2, which promotes generation of pseudopods required for phagocytosis. Phagocytosis may be terminated by the generation of ceramide which inhibits phospholipase D. The phospholipase D physiological product, phosphatidic acid, is able also to regulate the activity of type 1 phosphatidyl-1-phosphate-5-kinase, an enzyme that generates PI-(4,5)-P_2, thought to promote PMN degranulation through its ability to recruit lipid-binding proteins at the membrane.

The main function of human neutrophils is to combat infection and they are very well equipped to perform this task. This includes the presence of specific as well as more general antimicrobicidal systems. The antibacterial protein of bactericidal/permeabilty-increasing protein (BPI) is made only in neutrophils and stored in azurophilic granules. BPI binds LPS and is cytotoxic toward gram-negative bacteria, promoting their uptake by neutrophils, as well as destruction and detoxification of bacteria and endotoxin.

Phagocytic cells contain a NADPH dependent oxidase important for killing engulfed microbes. This oxidase transfers electrons from NADPH to O_2 to form $O_2^{\cdot}$ and consists of a membrane-bound flavocytochrome b composed of an α ($gp22^{phox}$) and β ($gp91^{phox}$) subunit. Three cytosolic proteins, $p40^{phox}$, $p47^{phox}$ and $p67^{phox}$, and a GTP-binding protein p21rac are required for activation of electron transport. Mutations in any of the genes encoding a component of the NADPH oxidase causes CGD, a rare immunodeficiency that can cause life-threatening infections. The majority of CGD patients suffer from the X-linked form of the disease caused by mutations in $gp91^{phox}$. Over the past 5 years the mutations in several hundred kindred of X-linked CGD families have been identified. These mutations lead to instability of $gp91^{phox}$ mRNA and/or protein. In spite of recent insights in the molecular underpinnings of CGD, little is known about the mechanisms leading to granulomata formation.

With the advent of a better understanding of the molecular mechanisms leading to NADPH oxidase activation, gene therapy is being attempted to correct the functional defect in O_2^- generation in CGD. A gene transfer approach is being also launched to treat patients with LAD, characterized by severe recurrent bacterial infection in which the phagocytic leukocytes fail to firmly adhere to endothelial cells and subsequently migrate to infectious sites. Molecular defects in the leukocyte integrin CD18 subunit are responsible for the failure to synthesize a CD18 subunit capable of forming heterodimers with the leukocyte integrin CD11 subunits and becoming inserted into the plasma membrane to mediate neutrophil adhesion to the endothelium. These gene therapy approaches look promising even though they are at a rather early stage, and several problems must be circumvented. Better vectors, other means for recruiting stem cells as well as mild suppression ("conditioning") of the patient's bone marrow with radiation to enhance engraftment of gene-corrected stem cells will be required.

Neutrophil functions have long been described, but a great advance in the knowledge at the molecular level of these functions has been obtained only during the last recent years. This workshop highlighted the rapid progress made over the last years in trying to dissect the molecular events occurring in the manifold functionality of these cells. *In vitro* and *in vivo* studies have revealed a great signaling cross-talk and complexity as well as pleiotropic effects of molecules and receptors in the different stages of neutrophil differentiation and activation. In addition, neutrophils contain specific components and display peculiar characteristics that make them as a unique and perfect weapon to fight rapidly infection, playing a major role in the surveillance system of host organism against foreign invaders and in acute inflammation. Future molecular studies are expected to reveal mechanisms that will enable us to improve and modulate neutrophil bactericidal and inflammatory responses.

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Molecular Clocks

Organized by
P. Sassone-Corsi and J. R. Naranjo

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Co-sponsored by the European Molecular Biology Organization

Circadian and seasonal rhythms are central to most biological systems, from daily oscillations in plant photosynthesis to hormone secretion and annual breeding cycles in mammals. All animals have an endogenous clock or *pacemaker*, which, independently from the day-night cycle, generates circadian rhythms in physiology and behaviour. For years researchers thought that these regulatory systems required an intact tissue organization and relied upon intercellular communications. Today we know that each cell composing the *pacemaker* has endogenous oscillatory properties and contains an autonomous clock.

During the past 10 years much attention has been given to the search for genes responsible for the clock function. Clock genes have been cloned in *Drosophila*, *Neurospora*, zebrafish and mammals. An emerging common feature is that most clock genes encode proteins with the structural characteristics of transcription factors, although there are notable exceptions. These transcription factors are characterized by the presence of PAS domains, a structural motif involved in protein-protein interactions. PAS domains take the name from the *Drosophila* PER gene, the mammalian Arnt (a dimerization partner of the dioxin receptor) and Sim, the product of the fly *single-minded* gene. In addition, a second general feature is that clock molecules operate within regulatory networks where autoregulatory feedback loops play a central role. The example of *Drosophila* PER and TIM - factors encoded by the *period* and *timeless* genes, respectively - represents a paradigm in the field.

The identification of molecular clock components has provided powerful tools to address fundamental biological questions such as: which cells contain clocks? When and how the clock starts ticking? How is it able to anticipate the light-dark cycle, and how is light able to directly influence clock function? These questions, and others, constituted the centre of debate during the recent "Molecular Clocks" meeting organized by the Juan March Foundation in Madrid, Spain. As a result, a base for consensus has been achieved for some of the major topics in clock function during these days of discussions. First, data from independent groups predicted the existence of extraretinal photoreceptors in mammals which would mediate entrainment of the clock to light-dark cycles, for instance reproductive responses to photoperiods. In this context, the identification of CRY1 and CRY2 in the mouse, which are homologs of plant blue light-receptors (cryptochromes) and photolyases, open a new avenue of understanding since they are expressed in tissues that are not commonly though to be light-sensitive. Second, clock genes have a generalized expression in various tissues, and analysis of their subcellular location and protein-protein interaction has established a greater complexity in the regulation and combinatorial functions of these factors in mammals. Third, oscillators are present in peripheral tissues and oscillation is kept in *ex vivo* organ cultures of these tissues. Furthermore, independent pacemakers can also be revealed in single cells where their oscillations can be influenced in different ways by agents acting on various intracellular signaling pathways.

Our understanding of the functioning of the circadian clock is progressing by leaps and bounds and the future will undoubtedly hold many surprises. Crucial questions are: what is the biological role of peripheral clocks? How does light entrain the clock? How do the molecular components of the clock work together and how are they modulated by intracellular pathways?.

J.R. Naranjo and P. Sassone-Corsi

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Molecular Nature of the Gastrula Organizing Center:
75 years after Spemann and Mangold

Organized by
E. M. De Robertis and J. Aréchaga

(24-26 May)

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and Human Development (USA)

Seventy-five years ago, in 1924, Hans Spemann and Hilde Mangold performed one of the best known experiments in embryology. They transplanted a small region of the amphibian gastrula embryo, the dorsal lip of the blastopore, into the opposite (ventral) side of a host embryo. They found that the graft, or "organizer", was able to induce a Siamese twin. The twinned axis was largely recruited from neighboring cells, indicating that vertebrate development takes place through a series of cell-cell inductions. Spemann's organizer had three activities:

1) It was able to induce central nervous system (CNS) on the overlying ectoderm.

2) It dorsalized the mesoderm, forming somite and muscle at the expense of neighboring cells that would normally form mesenchyme and blood.

3) It induced a secondary gut with all its endodermal derivatives such as liver and pancreas.

This experiment had an enormous impact on the biological thinking of the twentieth century. The organizer graft had to release substances responsible for the induction and patterning of the ecto-, meso- and endoderm, the three germ layers of the embryo. Isolating these inductive substances became the Holy Grail for experimental embryologists.

With the advent of molecular cloning, it became possible for researchers to isolate genes specifically expressed in Spemann's organizer and to study their properties. A number of genes were shown to function as transcription factors in the organizer, such as goosecoid, Lim-1, Xnot, Otx2, Siamois, Xanf-1, and HNF3-b. The function of these homeobox genes is to control the expression of secreted factors that in turn pattern the embryo. These secreted proteins include Noggin, Follistatin, Chordin, Frzb-1, ADMP, Dkk, Nodal-related, Cerberus and others.

Whereas some of this work started in Xenopus, mutagenesis screens in zebrafish identified mutations in organizer-specific genes such as Xnot (floating head) and chordin (chordino). In the mouse the homologues of most of the aforementioned genes have been inactivated by targeted gene mutation. In chick grafting experiments and implantation of beads expressing secreted factors have led to a renaissance of the study of gastrulation. Thus in 1999 the time was ripe to bring together a group of leaders in the field of vertebrate development to discuss recent progress, to integrate the information from diverse experimental animal models, and to discuss the questions that remained for future pursuit.

The workshop was not a celebration of the landmark Spemann experiment from a historical point of view but rather a discussion of the latest findings on the field. One of the unexpected results has been that many of the secreted molecules that pattern the embryo are themselves inhibitors of well-known growth factors, such as BMPs, Nodal-related genes and Wnts. These secreted antagonists act in the extracellular space and their activity can be controlled by proteolysis.

With so many components recently discovered, it was no surprise that the workshop did not provide final answers concerning the molecular nature of the gastrula organizer. Some aspects, however, seem to be well settled. For example, the recent genetic screens in zebrafish show that BMP

signals act at late gastrula to promote ventral development in the three germ layers. Studies in Xenopus have shown that the earliest signals are provided by beta-catenin, which promotes dorsal development already at early cleavage stages. During the intervening period - spanning from early cleavage to late gastrula - a plethora of molecules come into play and their exact functional relationships are being unraveled. Mouse knockouts revealed the unique and redundant function of the various genes, suggesting that we are only at the beginning of the dissection of the complexities of embryonic patterning. Studies in chick embryos pointed to the importance of cell movements and morphogenesis, an aspect that deserves much more attention than has been given to date. Studies in the diverse model systems provided a great synergy in understanding the common mechanisms of vertebrate gastrulation.

The workshop covered the latest aspects of the molecular biology of early patterning in vertebrates. The advances in the past few years have been astounding. New molecules and regulatory principles have been discovered. Some of the novel secreted factors will no doubt be useful to induce cell differentiation in vitro and may find applications in tissue replacement therapy. The gastrula organizer controls pattern formation of the vertebrate body plan and therefore, we can expect that Spemann's organizer will keep yielding new secrets well into its hundredth anniversary.

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Telomeres and Telomerase: Cancer, Aging and Genetic Instability

Organized by
M. A. Blasco

(7-9 June)

The extremists: telomeres, telomerase and associated partners

Incomplete duplication or aberrant segregation of chromosomes eventually compromises the proliferative potential of eukaryotic cells, limiting their life span. Increasing evidence indicates that the ends of chromosomes, or telomeres, have a fundamental role in both crucial moments of cell division. Telomere biology is essential to understand the molecular clocks underlying cell proliferation. Most importantly, proteins that act at the telomeres such as the enzyme telomerase and other telomere-associated proteins have become targets to control pathological aspects of cell division such as ageing or cancer. For these reasons, the structure and function of telomeres, as well as that of associated proteins, has become the focus of intense research during the last years. The role of telomerase components, telomerase-associated proteins and other telomere-binding proteins is being unravelled at the moment using both biochemical and genetic approaches.

In human cells, telomere length decreases proportionally to the number of times that a cell divides, presumably due to the incomplete replication of the DNA lagging strand. The rate of telomere shortening is 80 to 150 bps per cell. One of the key factors involved in regulating telomere is a reverse transcriptase called telomerase. Telomerase is a ribonucleoprotein DNA polymerase that is able to synthezise "de novo" telomeres onto chromosome ends. The construction and characterization of knock out strains for telomerase activity in different organisms has proven that telomerase is indeed essential to maintain telomeres and that the loss of telomeres is associated with genomic instability and the loss of cell viability. In mammals, telomere shortening has been associated to defects during embryonic development, in the germ line, and in the highly proliferative tissues of the adult. The precise regulation of telomerase during normal development tumor growth, however, remains unknown. The isolation of the different telomerase components together with the study of cell systems that lack telomerase will help to understand the regulation and function of this enzyme in mammals.

In yeast, deletion of the telomerase RNA gene leads to telomere shortening and, after a lag period of about 40 generations, to the loss of cell viability. It is possible to obtain "survivor" cells in yeast strains that have active recombination pathways and lack telomerase activity. In these survivors, telomeres are apparently lengthened via a recombination mediated gene conversion mechanism. Recent experiments suggest that a bypass mechanism for telomerase may also operate in mammalian cells. Telomerase-negative mammalian cell lines have been identified and in most cases the telomeres are elongated to 2 or 3 times their normal size. The identification of telomerase-independent telomere maintenance in mammalian cells is essential to understand telomere biology. The study of mouse strains deficient for telomerase activity and/or DNA recombination or DNA repair proteins will help to identify these mechanisms and to establish their physiological relevance.

All these different aspects of telomere biology have been the subject of the current March Foundation Workshop "Telomeres and telomerase: cancer, aging and genetic instability". This meeting has provided a forum were recent discoveries have been reported and discussed by the telomere and telomerase scientific community.

María A. Blasco

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Specificity in Ras and Rho-Mediated Signalling Events

Organized by
J. L. Bos, J. C. Lacal and A. Hall

(4-6 October)

Ras and Rho are the founder-members of two families of small GTPases, each with more than ten members, which function in signal transduction from plasma membrane bound-receptors to cellular responses. The original "dogma" was that Ras and the Ras-like members control signalling cascades involved in cell growth and cell differentiation, whereas Rho-like GTPases control signalling towards cell architecture and motility. A substantial amount of research has focussed on these lines for the last 15 years. However, recently we have learned that signalling in which these small GTPases are involved, is much more broad and complicated than originally anticipated. Thus, there is now a large body of evidence demonstrating that Ras-like and Rho family members play a role in the control of transcription and the regulation of the cell cycle. Indeed, Ras and Rho proteins may impinge in a variety of cell responses such as cell growth and differentiation, senescence, cell death, development, motility, invasion and many others. Frequently, Ras and Rho GTPases co-operate in these processes by a complex network of cross-talking pathways. However, we have learned that each GTPase have its own peculiarities, with respect to structure, biochemical properties, localisation, etc. For instance, several Ras-like proteins have virtually similar effector domains as Ras, but their function appears to be completely different. A similar situation can be found with the Rho-like GTPases, with a large number of partners/effectors identified thus far. This is even further complicated by the still-growing number of potential effectors for each member of the Ras and Rho branches. Thus, it seems that besides a high degree of cross-talking among members of these two families of GTPases, there are still differences in the final biological end-points for specific members of the two families. Most effects measured thus far have been generated using vastly overexpressed systems. This is a valid approach to get an idea who is talking to who, and the relative hierarchy for each process, but the next step has to be more precise. This meeting has been called in an attempt to foster our understanding of the specific involvement of each family in biological end points, gathering a group of people who can specifically address the above issues from different sides.

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The Interface between Transcription and DNA Repair, Recombination and Chromatin Remodelling

Organized by
A. Aguilera and J. H. J. Hoeijmakers

(18-20 October)

Transcription of DNA is a central process in the cell and obviously essential for all living systems. It is a key regulatory mechanism in development and differentiation and the most important focal point of signal transduction and other regulatory networks controlling the response to exogenous and endogenous signals. The transcription process allows fine-tuning of gene expression and is the crucial stage where the "on/off" decision is made. Many disease states, including cancer, involve dysregulation of gene expression.

Due to its fundamental importance, elucidation of the molecular mechanism of the process of transcription and its regulation is one of the most intensively studied fields of research in today's biology. As a result of the massive, world-wide investment of research activities impressive progress has been made concerning the insight into the basal mechanism of transcription initiation and the interplay between the basal transcription machinery and the regulatory circuit. The basic transcription reaction has been dissected and reconstituted in vitro from purified components. Different factors with multiple specialized functions accomplish the complex series of events from transcription initiation to elongation and termination. Numerous interactions with regulatory proteins have been identified.

Recently, converging developments have triggered the notion that transcription has multiple links with other cellular processes that involve DNA homeostasis, notably DNA damage and repair, recombination and chromatin dynamics. Several examples illustrate the molecular intricacies and biological impact of these interphases.

1. An important connection between transcription and DNA repair was revealed by the discovery of a distinct DNA repair pathway focussing on removal of DNA lesions that obstruct ongoing transcription. This transcription-coupled repair process is intimately connected with the nucleotide excision repair system, that eliminates a wide range of lesions from the genome, including damage induced by ultraviolet light and by numerous chemical agents.

2. Another example of a connection between transcription and DNA repair is the dual functional factor TFIIH, that is involved in transcription initiation as well as in nucleotide excision repair. Importantly, mutations in this multi-subunit factor can give rise to three distinct conditions all associated with photosensitivity: the skin cancer-prone syndrome xeroderma pigmentosum with or without the hallmarks of Cockayne syndrome and the severe neuro-developmental disorder thrichothiodystrophy characterized by brittle hair and nails. The latter two diseases reveal a novel concept in human genetics: the existence of inborn defects in basal transcription.

3. Another intriguing link between transcription and DNA homeostasis is the observation of increased mutation rates associated with transcription. This phenomenon has a good example in the poorly understood mechanism of hypermutation in active immunoglobulin genes, that enhances antibody diversity. Interestingly, an increase of mutation rates has also been observed associated with transcriptional activation of genes in yeast.

4. Recombination rates are increased by transcriptional activation, in prokaryotes and eukaryotes from yeast to mammals. Intriguingly, several reports suggest that transcriptional elongation defects can also be linked to an increase in recombination.

5. Finally, both DNA repair and recombination have been shown to be modulated by different states of chromatin structure whereas transcription is also intimately linked with chromatin fluidity.

The above examples likely represent the tip of an iceberg. Probably, numerous ramifications of transcription, repair, recombination and chromatin conformation with each other as well as with other cellular events have yet to be discovered. This workshop has provided a forum where recent discoveries have been reported and discussed in an effort to integrate the knowledge of the individual areas with each other and to improve our understanding of the molecular basis and biological impact of these fascinating connections.

A. Aguilera and J.H.J. Hoeijmakers

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Dynamics of the Plant Extracellular Matrix

Organized by
K. Roberts and P. Vera

(11-13 November)

Plant cells have evolved and retained at every stage of the cell cycle a complex extracellular matrix (ECM). The acquisition of this distinct ECM compartment is central to an explanation of the differences between plant and animal cell development. Because of its presence, plants have evolved a distinctly different mode of multicellular construction characterized by incomplete cell cleavage, continuous cytoplasmic connections, and absence of cell motility during morphogenesis. Therefore, the ECM of a differentiating plant cell is specifically adapted to the particular function of that cell type. Moreover, developmental events and exposure to any of a number of abiotic and biotic stresses further increase the compositional and structural variation of the ECM.

The plant ECM also plays important roles during pathogenesis because it is the place where the first host-pathogen interaction and recognition events take place, and where rapid cellular responses are executed in the form of local modification and signal transmission that set in motion subsequent transcriptional activation of defense-related genes.

The cell wall, by far the major component of the plant ECM, is also very dynamic and helps confer unique and distinctive features to plant cells. The construction and architecture of the cell wall varies in an orderly manner in accordance with the developmental stages of cells. This pliable character of cell walls is a direct consequence of changes in the proportion and degree of assembly of various structural polysaccharides, including cellulose microfibrils, pectin, and hemicellulose polymers. Also, differences between cell walls of defined cell types originate as a consequence of deposition of more specific polymers with defined functions (e.g., lignin, which serves to harden and stiffen the walls of tracheary elements).

Plant cell walls also contain structural proteins that participate in the flexible integration of environmental responses within plastic developmental programs. The genes encoding these structural proteins are tightly regulated, and their expression shows cell type specificity and developmental regulation. Collectively, it seems that plants have evolved regulatory mechanisms allowing genes encoding structural cell wall proteins to be expressed specifically and in accord with the different functions exerted by the different tissues. The expression of genes encoding some of these cell wall proteins can be altered by different cues (e.g., wounding, elicitor treatment, or pathogen attack), and the deposition of the encoded proteins in the cell wall results in alterations of the functional properties of this compartment.

Since it is increasingly apparent that cell-cell and cell-matrix interactions exert important influences upon gene expression and the development of cellular phenotypes in plants, the characterization of new molecules and signalling events in the plant ECM that could eventually participate in certain critical features of the plant lifestyle, either under normal or pathogenesis-related situations, are relevant to gain understanding of the importance of this extracellular cell compartment in plants.

This workshop brought together scientists actively engaged in the characterization and understanding of the plant ECM using different systems and with physiological, biochemical, molecular and cellular biology as well as genetic approaches. The workshop provided a unique opportunity for the participants to exchange and share information, to review and discuss new approaches, and to propose directions for future research.

Keith Roberts and Pablo Vera

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Helicases as Molecular Motors in Nucleic Acid Strand Separation

Organized by
E. Lanka and J. M. Carazo

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Double helical nucleic acid is known for its stability, and yet for most critical transactions during the cell cycle such as replication, transcription, recombination and repair, and DNA transfer during bacterial conjugation, the two complementary strands of the duplex must be separated, at least transiently. Strand separation is achieved by helicases.

Helicases are motor proteins which couple nucleotide (NTP) binding and hydrolysis to nucleic acid unwinding. Almost 25 years ago enzymes of this class were originally named and described as chemo-mechanical agents for the control of DNA structure by Hoffmann-Berling (Heidelberg, Germany). Since then helicases have been the subject of extensive biochemical investigations which have shed light into the complex interplay between NTP and/or nucleic acid binding, and nucleic acid unwinding.

The attraction to study the function of helicases of the cell life cycle increased considerably by the discovery of helicase-related mammalian diseases, like Xeroderma Pigmentosum, Werner's syndrome, and Bloom's syndrome. However the progress in understanding mechanistic principles of strand separation is still guided by research on prokaryotic enzymes. A large variety of helicases is known, twelve in *E. coli* and about 140 are expected for yeast. However, not all of them are essential for cell viability. In this context we like to mention the importance of the replicative helicase DnaB of *E. coli*. The DnaB protein, the function of which was discovered in 1986 by McMacken, has been the subject of intense study over the last two decades and still is one of the most important model systems. However, the work on the replicative helicase of *E. coli* has been greatly inspired by work on corresponding proteins of the replication systems of the lytic bacteriophages T4 and T7.

The organization of this first workshop entirely dedicated to helicases was determined by questions concerning the structure-function relationship of nucleic acid unwinding machines. The multidisciplinary approach to the field by the combination of ideas of geneticists, biochemists, biophysicists and structural biologists was supposed to integrate the comprehensive knowledge with very recent developments on helicases into models on the mechanism of unwinding. Since structural data provide a new discussion level for explanations in enzymology, the workshop became timely appropriate when the first crystal structures of a monomeric and dimeric helicase (PcrA of *B. stearothermophilus* and Rep of *E.coli*) were published.

The discussion of structural data of monomeric, dimeric and hexameric helicases comprised the first part of workshops leading into the evaluation of mechanistic principles and culminating in the discussion of helicases in the interplay with other components in replication, recombination and repair, transcription, and bacterial conjugation. The latter of the three sections was thought to provide insight also into the large variety of helicases in general.

Highlights of the discussions were certainly the novel information on crystal structures of hexameric replicative helicases extending earlier data obtained by electron microscopy. These data provide insight into the dynamics of the helicase/substrate interaction in the form of "snap shots". As a consequence, the need to expand on these approaches became obvious. In particular, it is critical to obtain structures of complexes between helicases and nucleic acids, substrates and inhibitors. Another important issue that still needs additional attention are biophysical studies of the molecular dynamics of helicases.

Thus, based on the speed of progress seen in the field at the occassion of this first helicase workshop, we look forward with great expectations, in particular to a new helicase meeting which will probably be held sometime in the near future.

Erich Lanka & José Maria Carazo

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The Neural Mechanisms of Addiction

Organized by
R. C. Malenka, E. J. Nestler and F. Rodríguez de Fonseca

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Drug addiction is a medical illness that has devastating health, social, political and economic consequences. Indeed, it is one of the most important health problems facing the world today. Addiction has this devastating impact despite extensive political effort and social/behavioral research aimed at its reduction. Social and psychological approaches to the treatment of addiction - while beneficial to many - have been only partially successful in alleviating the worldwide burden of substance abuse.

Based on recent scientific advances, attitudes toward addiction and approaches to its treatment and prevention are rapidly changing. It is now clear that addiction should be conceptualized as a brain disease that occurs in susceptible individuals as a consequence of cellular and molecular changes in nervous system function. It is well established that certain brain circuits, like those involving mesencephalic dopaminergic neurons, are particularly important for mediating the behavioral and psychological actions of drugs of abuse. This has led to the development of more sophisticated molecular hypotheses to explain critical features of addiction such as sensitization, tolerance, withdrawal and dependence. Genetic studies in inbred strains of rodents and the achievement of genetically modified animals have facilitated the identification of these molecular targets of major abused drugs. Illustrating this approach, quantitative trait locus mapping has established strong associations between alcohol preference drinking and specific chromosomal regions containing the genes for the serotonin 1_B receptor, the dopamine D_2 receptor or the GABA-A receptor g_2 subunit, while gene targeting in mice identified the Φ-opioid receptor and the dopamine D2 receptor as necessary elements for the morphine-induced reward.

Additionally, other molecular mechanisms, recruited by drug stimulation as a second stage in cellular signaling, have been found to contribute to the acute and chronic effects of drugs. Specifically , second messengers such as cAMP and specific transcriptions factors such as FosB and CREB participate in the transition to the drug-dependence status resulting from repeated drug exposure. The actions of these transcription factors on specific genes such as those coding for voltage-gated channels or local mechanisms regulating synaptic transmission such as those involved in neurotransmitter storage and release contribute to the adaptive plastic alterations in synaptic transmission in reward-relevant circuits characterized in drug-dependent animals. The convergence of multiple transmitter systems in reward-relevant synapses (such as glutamate, acetylcholine or endocannabinoids) have been also identified as mechanisms contributing to the psychoactive effects of abused drugs.

Different forms of synaptic plasticity, including long-term depression and long-term potentiation, have been described in the main synapses of the reward-processing circuitry, including the nucleus accumbens and the ventral tegmental area. These synaptic modifications may also contribute to the neural adaptations that mediate addiction. Drug-induced plasticity is further modified by environmental factors that may amplify drug effects, eventually leading to marked morphological changes in reward-relevant synapses. Yet another common and important consequence of abused drugs is activation of the physiological stress response leading to the release of glucocorticoids. These hormones are activators of a family of transcription factors that regulate the expression of specific genes in the brain and may also contribute to the neuroadaptions underlying addiction.

Thus, studies on the cellular, biochemical and molecular adaptions that occur in the brain following acute and chronic exposure to drugs of abuse indicate that drugs and drug-associated experiences converge to modify critical neural circuitry and configure the phenotype of the drug-vulnerable subject. The physical and dynamic alterations in the circuits that process motivation and emotion are likely critical substrate for the long-term changes in behavior that are characteristic of drug users: conditioning, reward expectancy, loss of control of drug intake, drug craving and relapse. The main neural circuits that process these different elements of addictive behavior have been elucidated. One of the most important circuits is the mesolimbic dopaminergic system which appears to be critically important for processing reward information and the motivational salience of external objects and events. This system is activated by all drugs of abuse, as well as drug-associated stimuli.

These findings and hypothesis, based on work using laboratory animals have allowed the establishment of neurobiological models of drug addiction that can be verified or disproven in human studies. In fact, preliminary functional brain imaging analysis of the effects of drugs of abuse on the brains of addicted (and non-addicted) subjects has generally confirmed this model in which drugs with distinctly different chemical structures and initial molecular targets may ultimately activate the same "final common pathways" in the brain. The further elucidation of the adaptive changes that occur in these pathways in response to drugs of abuse and which ultimately lead to addiction should enormously facilitate efforts to diminish the dire medical and societal consequences of this chronic brain disorder.

R. C. Malenka, E. J. Nestler and F. Rodríguez de Fonseca

LIST OF INVITED SPEAKERS

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1999 Fellowships

1999 FELLOWSHIPS

In meetings organized by the Centre a limited number of fellowships is normally offered to participants, in order to help them cover at least part of their travel and accommodation expenses.

These fellowships are usually awarded to the younger scientists selected for participation, or to scientists coming from countries where availability of funds is particularly scarce.

During 1999, 116 of these fellowships were awarded to participants in 13 different meetings. Among these, 34 fellowships were granted to scientists working in Spain, and 82 to scientists working abroad.

XVIII Juan March Lectures

The Juan March lectures were first organized in 1982, and since then have been held every year without interruption. The purpose of these lectures is to put Spanish students and professionals in the field of Biology in direct contact with some outstanding world figures. The invited lecturers often take advantage of their visit to Spain to give additional seminars in different laboratories.

In 1999, the XVIII lectures series took place, with the general theme of **NEW PERSPECTIVES IN CANCER RESEARCH**. The speakers and topics were as follows:

1 March
J. MICHAEL BISHOP
Department of Microbiology and Immunology
University of California
San Francisco, California (USA)
1989 Nobel Prize in Medicine

Cancer: the rise of the genetic paradigm.

Introduced by: **Margarita Salas**
Centro de Biología Molecular "Severo Ochoa"
Madrid

8 March
RICHARD PETO
Clinical Trial Service Unit &
Epidemiological Studies Unit
University of Oxford
Oxford (UK)

Worldwide strategies for cancer control.

Introduced by: **Manuel Nieto-Sampedro**
Instituto Cajal
Madrid

15 March
TERRY H. RABBITTS
Laboratory of Molecular Biology
Medical Research Council
Cambridge (UK)

Chromosomal translocations, cancer and therapeutic targets.

Introduced by: **Andrés Aguilera**
Facultad de Biología
Universidad de Sevilla

22 March
MARIANO BARBACID
Centro Nacional de Investigaciones
Oncológicas Carlos III
Madrid

Cancer and the cell cycle.

Introduced by: **Juan Carlos Lacal**
Instituto de Investigaciones Biomédicas
Madrid

Sessions Open to the Public

In connection with some workshops, prominent invited speakers have given additional lectures in sessions open to the public. In 1999, these were as follows:

During the workshop on **Molecular clocks** (10-12 May):

- **MICHAEL MENAKER**
  NSF Center for Biological Timing
  Charlottesville, VA. (USA)

Biological clocks: from molecules to man

Introduced by: **Paolo Sassone-Corsi**
IGBMC
Université Louis Pasteur
Strasbourg (France)

During the workshop on **The interface between transcription and DNA repair, recombination and chromatin remodelling** (18-20 October):

- **JAN H. J. HOEIJMAKERS**
  Erasmus University
  Rotterdam (The Netherlands)

Cancer, aging and the condition of our genes

Introduced by: **Andrés Aguilera**
Facultad de Biología
Universidad de Sevilla (Spain)

During the workshop on **Helicases as molecular motors in nucleic acid strand separation** (20-22 November):

- **JOHN E. WALKER**
  MRC
  Dunn Human Nutrition Unit
  Cambridge (UK)
  1997 Nobel Prize in Chemistry

Biological energy conversion

Introduced by: **Erich Lanka**
Max-Plank-Institut für Molekulare Genetik
Berlin (Germany)

During the workshop on **The neural mechanisms of addiction** (13-15 December):

ROBERT C. MALENKA
Department of Psychiatry and Behavioral Sciences
Stanford University School of Medicine
Palo Alto, CA. (USA)

Basic mechanisms of synaptic plasticity

Introduced by: **Fernando Rodríguez de Fonseca**
Facultad de Psicología
Universidad Complutense de Madrid (Spain)

Reviews in Scientific Journals

During 1999 the meetings organized by the Centre have been reviewed in the following articles:

- Vicente, M., Chater, K. F. and de Lorenzo, V. (1999). Bacterial transcription factors involved in global regulation. **Molecular Microbiology 33 (1): 8-17**. (On the workshop of the same title, held in June 1998).

- Glimcher, L. H. and Singh, H. (1999). Transcription factors in lymphocyte development — T and B cells get together. **Cell 96: 13-23**. (On the workshop *Transcription factors involved in lymphocyte development and function*, held in October 1998).

- Rivas, L. and Ganz, T. (1999). Eukaryotic antibiotic peptides: not only a membrane business. **Drug Discovery Today 4 (6): 254-256**. (On the workshop *Eukaryotic antibiotic peptides*, held in February 1999).

- Dever T. E. (1999). Translation initiation: adept at adapting. **Trends in Biochemical Sciences 24: 398-403**. (On the workshop *Regulation of protein synthesis in eukaryotes*, held in March 1999).

- Inzé, D., Gutiérrez, C. and Chua, N-H. (1999). Trends in plant cell cycle research. **The Plant Cell 11 (1): 991-994**. (On the workshop *Cell cycle regulation and cytoskeleton in plants*, held in March 1999).

- Mollinedo, F., Borregaard, N., and Boxer, L. A. (1999). Novel trends in neutrophil structure, function and development. **Immunology Today 20 (12): 535-537**. (On the workshop *Neutrophil development and function*, held in April 1999).

- Foulkes, N. S., Naranjo, J. R. and Sassone-Corsi, P. (1999). Setting the clock in Madrid. **Trends in Cell Biology 9: 371-372**. (On the workshop *Molecular clocks*, held in May 1999).

- Nieto, M. A. (1999). Reorganizing the Organizer 75 years on. **Cell 98: 417-425.** (On the workshop *Molecular nature of the gastrula organizing center: 75 years after Spemann and Mangold*, held in May 1999).

- Blasco, M. A., Gasser, S. M. and Lingner, J. (1999). Telomeres and telomerase. **Genes and Development 13: 2353-2359**. (On the workshop *Telomeres and telomerase: cancer, aging and genetic instability*, held in June 1999).

- Waksman, G., Lanka, E. and Carazo, J.-M. (2000). Helicases as nucleic acid unwinding machines. **Nature Structural Biology 7 (1): 20-22.** (On the workshop *Helicases as molecular motors in nucleic acid strand separation*, held in November 1999).

Editors of the following major scientific journals have participated in different meetings of the Centre during 1999: **Cell** (in two meetings); **Nature** (in two meetings); **Science**; **Neuron** (in two meetings); **Nature Neuroscience** (in two meetings).

2000 Meetings Schedule

CENTRE FOR INTERNATIONAL MEETINGS ON BIOLOGY
2000 MEETINGS SCHEDULE

Date	Meeting Subject	Organizers
28 February-1 March	**The Molecules of Pain: Molecular Approaches to Pain Research**	**S.P. Hunt.** University College London. **F. Cerveró.** Universidad de Alcalá. Madrid.
13-15 March	**Control of Signalling by Protein Phosphorylation**	**J. Schlessinger.** NYU Medical Center. New York. **G. Thomas.** Friedrich Miescher Institute. Basel. **F. de Pablo.** Centro de Investigaciones Biológicas. Madrid. **J. Moscat.** Centro de Biología Molecular "Severo Ochoa". Madrid.
27-29 March	**Biochemistry and Molecular Biology of Gibberellins**	**P. Hedden.** University of Bristol. **J.L. García-Martínez.** Instituto de Biología Molecular y Celular de Plantas. Valencia.
10-12 April	**Integration of Transcriptional Regulation and Chromatin Structure**	**J.T. Kadonaga.** University of California. San Diego. **J. Ausió.** University of Victoria. **E. Palacián.** Centro de Biología Molecular "Severo Ochoa". Madrid.
8-10 May	**Tumor Suppressor Networks**	**J. Massagué.** Memorial Sloan-Kettering Cancer Center. New York. **M. Serrano.** Centro Nacional de Biotecnología. Madrid.
22-24 May	**Regulated Exocytosis and the Vesicle Cycle**	**R.D. Burgoyne.** University of Liverpool. **G. Alvarez de Toledo.** Facultad de Medicina. Universidad de Sevilla.
* 5- 7 June	**Dendrites**	**S. Siegelbaum.** Columbia University. New York. **R. Yuste.** Columbia University. New York.
19-21 June	**The Myc Network: Regulation of Cell Proliferation, Differentiation and Death**	**R.N. Eisenman.** Fred Hutchinson Cancer Research Center. Seattle. **J. León.** Facultad de Medicina. Universidad de Cantabria. Santander.
2- 4 October	**Regulation of Messenger RNA Processing**	**W. Keller.** University of Basel and Biozentrum. Basel. **J. Ortín.** Centro Nacional de Biotecnología. Madrid. **J. Valcárcel.** European Molecular Biology Laboratory. Heidelberg.
16-18 October	**Genetic Factors that Control Cell Birth, Cell Allocation and Migration in the Developing Forebrain**	**P. Rakic.** Yale University. New Haven. **E. Soriano.** Facultad de Biología. Universidad de Barcelona. **A. Alvarez-Buylla.** Rockefeller University. New York.
6- 8 November	**Chaperonins: Structure and Function**	**W. Baumeister.** Max--Planck-Institute for Biochemistry. Munich. **J.M. Valpuesta.** Centro Nacional de Biotecnología. Madrid. **J.L. Carrascosa.** Centro Nacional de Biotecnología. Madrid.
27-29 November	**Comparison of the Mechanisms of CellularVesicle and Viral Membrane Fusion**	**J.J. Skehel.** National Institute for Medical Research. London. **J.A. Melero.** Centro Nacional de Biología Fundamental. ISCIII. Madrid.
11-13 December	**Molecular Approaches to Tuberculosis**	**B. Gicquel.** Institut Pasteur. París. **C. Martín.** Facultad de Medicina. Universidad de Zaragoza.

*** This meeting will take place at Columbia University, New York. All others will be organized at the Instituto Juan March, Madrid.**

Index of Personal Names

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The **Fundación Juan March** is a private, non-profit making institution established in 1955 by the Spanish financier Juan March Ordinas.

It has organized more than 400 *art exhibitions* in Spain and abroad. Some 500 artists and researchers have received grants from the Foundation for creative or research projects in the fine arts. The Foundation's art collections are exhibited in the Museo de Arte Abstracto Español, in Cuenca; in the Museu d'Art Espanyol Contemporani, in Palma de Mallorca; in the Foundation's headquarters in Madrid, and also in travelling exhibitions.

In the field of *music*, the Foundation regularly organizes series of monographic concerts, didactic concerts for the young people (attended each year by approximately 25,000 students), commemorative concerts in honour of major musical figures, as well as concerts of a variety of other types. In total, more than 200 concerts are organized each year.

Two *libraries*, with specialized collections in Spanish Contemporary Theatre and Spanish Contemporary Music, are housed in the Foundation's headquarters. More than 50 lectures, seminars and courses are organized there each year, on a wide range of subjects.

The Foundation publishes a monthly Bulletin as well as "Saber/Leer", an illustrated book review. Annual reports, catalogues, leaflets and other publications are issued on a non-periodical basis.

The **Instituto Juan March de Estudios e Investigaciones** was established in 1986 as a private Foundation to support research and post-graduate studies in scientific fields, by means of specialised Centres of Advanced Study.

In 1987 the *Centre for Advanced Study in the Social Sciences* was created within the Juan March Institute to contribute to the extension of social scientific knowledge through the promotion of research, post-graduate teaching, and exchanges of researchers.

In 1992 the *Centre for International Meetings on Biology* was established to promote close cooperation and interaction among Spanish and foreign scientists working in the field of Biology, through workshops, courses, lectures, seminars and symposia.

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