Instituto Juan March
de Estudios e Investigaciones

90

CENTRO DE REUNIONES
INTERNACIONALES SOBRE BIOLOGÍA

1998
Annual Report

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1998
Annual Report

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

The most beautiful experience we can have is the mysterious. It is the fundamental emotion that stands at the cradle of true art and true science.

Albert Einstein. "The world as I see it", 1931.

INSTITUTO JUAN MARCH DE ESTUDIOS E INVESTIGACIONES

CENTRE FOR INTERNATIONAL MEETINGS ON BIOLOGY

1998 ANNUAL REPORT

CONTENTS

FOREWORD

This publication covers the activities of the Centre for International Meetings on Biology during the year 1998. 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 1998 was the organization of fourteen 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, 281 speakers were invited to the 1998 meetings, and 408 participants were chosen from among the 676 applications received.

14 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 1998, a tradition in the Centre since 1982. Information on these lectures is also included in the following pages. Another two sessions open to the general public were held to coincide with meetings mentioned above.

A short notice is given on reviews published during 1998 in scientific journals and books, regarding meetings organized by the Centre.

The schedule of meetings to take place in 1999 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 on 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
Medical Research Council, Cambridge. United Kingdom.

Margarita Salas
Centro de Biología Molecular. CSIC - Universidad
Autónoma de Madrid (Spain)

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**.

1998 Meetings Schedule

CENTRE FOR INTERNATIONAL MEETINGS ON BIOLOGY
1998 MEETINGS SCHEDULE

Date	Meeting Subject	Organizers
9-11 February	**Initiation of Replication in Prokaryotic Extrachromosomal Elements**	**M. Espinosa.** Centro de Investigaciones Biológicas. Madrid. **R. Díaz-Orejas.** Centro de Investigaciones Biológicas. Madrid. **D.K. Chattoraj.** Laboratory of Biochemistry. NIH-NCI. Bethesda. **E.G.H. Wagner.** The Swedish Univ. of Agricultural Sciences. Uppsala.
23-25 February	**Mechanisms Involved in Visual Perception**	**J. Cudeiro.** Dept. de Ciencias de la Salud I. Universidad de A Coruña. **A.M. Sillito.** Institute of Ophthalmology. London.
9-11 March	**Notch/Lin-12 Signalling**	**A. Martínez Arias.** Department of Zoology. University of Cambridge. **J. Modolell.** Centro de Biología Molecular "Severo Ochoa". Madrid. **S. Campuzano.** Centro de Biología Molecular "Severo Ochoa". Madrid.
30 March/1 April	**Membrane Protein Insertion, Folding and Dynamics**	**J.L.R. Arrondo.** Facultad de Ciencias. Univ.d del País Vasco. Bilbao. **F. M. Goñi.** Facultad de Ciencias. Universidad del País Vasco. Bilbao. **B. de Kruijff.** Centre for Biomembranes. Utrecht University. **B. A. Wallace.** Department of Crystallography. University of London.
20-22 April	**Plasmodesmata and Transport of Plant Viruses and Plant Macromolecules**	**F. García-Arenal.** E.T.S.I. Agrónomos. Univ. Politécnica de Madrid. **K.J. Oparka.** Scottish Crop Research Institute. Invergowrie, Dundee. **P. Palukaitis.** Scottish Crop Research Institute. Invergowrie, Dundee.
11-13 May	**Cellular Regulatory Mechanisms: Choices, Time and Space**	**S. Moreno.** Instituto de Microbiología Bioquímica. Univ. de Salamanca. **P. Nurse.** Imperial Cancer Research Fund. London.
25-27 May	**Wiring the Brain: Mechanisms that Control the Generation of Neural Specificity**	**R. Gallego.** Insstituto de Neurociencias. S. Juan, Alicante. **C. S. Goodman.** University of California, Berkeley.
11-13 June	**Bacterial Transcription Factors Involved in Global Regulation**	**M. Vicente**. Centro de Investigaciones Biológicas. Madrid. **A. Ishihama.** National Institute of Genetics. Mishima. **R. Kolter.** Harvard Medical School. Boston.
22-24 June	**Nitric Oxide: From Discovery to the Clinic**	**S. Lamas.** Centro de Investigaciones Biológicas. Madrid. **S. Moncada.** The Wolfson Institute. University College London.
5-7 October	**Chromatin and DNA Modification: Plant Gene Expression and Silencing**	**M.A. Vega-Palas**. Inst. de Bioquímica Vegetal y Fotosíntesis. Sevilla. **T.C. Hall.** IDMB. Texas A & M University. College Station. **A. P. Wolffe.** National Institutes of Health. Bethesda. **R.J. Ferl.** Department of Biotechnology. Univ. of Florida. Gainesville.
19-21 October	**Transcription Factors in Lymphocyte Development and Function**	**J.M. Redondo.** Hospital de la Princesa. Univ. Autónoma de Madrid. **P.D. Matthias.** Friedrich Miescher Institute. Basel. **S. Pettersson.** Karolinska Institute. Huddinge.
16-18 November	**Novel Approaches to Study Plant Growth Factors**	**A.F. Tiburcio.** Facultad de Farmacia. Universidad de Barcelona. **J. Schell**. Max-Planck-Institut für Züchtungsforschung. Köln.
30 Nov/2 Dec	**Structure and Mechanisms of Ion Channels**	**J. Lerma.** Instituto Cajal. Madrid. **N. Unwin.** Medical Research Council. Cambridge. **R. MacKinnon.** The Rockefeller University. New York.
14-16 December	**Protein Folding**	**M. Rico.** Instituto de Estructura de la Materia. Madrid. **A.R. Fersht.** Chemical Laboratory. Cambridge University. **L. Serrano**. European Molecular Biology Laboratory. Heidelberg.

Initiation of Replication in Prokaryotic Extrachromosomal Elements

Organized by
M. Espinosa, R. Díaz-Orejas, D.K. Chattoraj and E.G.H. Wagner

(9-11 February)

Bacteria are at the origin of life on earth. Basic mechanisms that were found and developed in microorganisms served the role of the main theme in the many variations played during cellular evolution. At the core of cellular proliferation is the copying (replication) of its genetic material. This is an essential process that requires efficiency and fidelity and that is regulated to prevent either the loss or the overproduction of the essential genetic information in the descendants. The elucidation, by Watson and Crick, of the structure of DNA, the macromolecule in which genetic information is stored, opened the way to the molecular characterization of its replication: DNA is normally formed by two strands that are complementary and that form a double helix. In the replication process each one of these complementary strands separate and serve as the template for the synthesis of the other. However, DNA replication does not occur spontaneously: it is the result of the action of DNA polymerases and other replication factors that catalize the process with high efficiency and accuracy. The functional-structural characterisation of these catalizers is a formidable task that started with the identification of DNA polymerases by A. Kornberg and that still continues. This workshop is a case in this search focusing on replication of prokaryotic extra chromosomal genetic elements: plasmids and bacteriophages (phages).

These elements are molecular "parasites" that propagate at the expense of bacteria but could also enrich the genetic contents of the host. Phages can have an extra-bacterial life because they can enclose DNA within a protein capsid. Plasmids lack this ability and they have an intracellular life in peace with the host. The greater autonomy of bacteriophages is reflected in a greater (or sometimes complete) independence from the host replication machinery. The peaceful coexistence of plasmids within their hosts is the result of complex regulatory mechanisms that couple plasmid replication to the bacterial cell cycle.

These genetic elements can incorporate new genetic material by different mechanisms and can also transfer it to new hosts either by infection (phage) or by conjugative mechanisms (plasmid). Therefore, plasmids and phages serve the role of genetic vectors in bacterial populations (or in biotechnological applications) and contribute to maintain and expand new abilities in these populations.

DNA replication has three clearly differentiated stages: initiation, elongation and termination. Initiation of DNA replication is the critical step at which the process starts, but also the stage at which the mechanism and the direction of replication as well as the regulation of the process are determined. The starting point of replication is usually determined by specific proteins (initiators) and by specific DNA sequences (origin).

Sometimes activation of the initiator or the initiation complex by chaperones is required in some plasmid and phage systems. The interaction of initiator proteins with the origin of replication can cause a conformational change that could expose particular regions of the protein for interaction with host replication factors. In some cases, initiator interactions with spatially separate sites have been reported in phages and also in plasmids, but usually initiation starts from a fixed origin.

DNA polymerases are unable to start "de novo" synthesis of DNA. The incorporation of the first nucleotide (building block) by DNA polymerases requires a template and a primer: the latter can be provided by a protein (protein-primed replication), a DNA (rolling circle replication,

initiation by DNA strand invasion) or an RNA (theta-type replication). DNA polymerases include also a read-proof exonuclease activity that allows the discrimination and eventual correction of mis-incorporated nucleotide at the end of the nascent chain. This general feature is also maintained in DNA polymerases able to use a protein primer: in these systems a slide-back mechanism makes possible the proofreading of the first nucleotide incorporated.

It is assumed that incorporation of DNA polymerases at the replication fork completes the assembly of the replication complex (replisome). The replisome could include, in addition to activities to prime and synthesize DNA (primase and DNA polymerase), other activities needed to open the DNA strands ahead of the polymerase which are provided by DNA helicases. Specific topoisomerases can solve the torsional stress produced by the unwinding of DNA strands ahead of the replication fork and single stranded DNA binding proteins can stabilize single stranded regions exposed in replicating intermediates. Removal of the RNA primers, replacement of these by DNA segments and ligation of the DNA pieces are also required during replication and these activities are catalyzed by different enzymes.

Termination of DNA replication is achieved by different strategies depending on the topology of the DNA template (lineal versus circular) and on the mechanisms of initiation (rolling circle versus theta replication in circular templates; initiation from internal sites or via terminal protein in linear templates).

Blockage of DNA replication can occur due to the action of particular loaders of replication initiation factors or by the explicit action of proteins that inactivate replication initiation factors. Re-assembling of the initiation complexes modulated by chaperones or specific neutralization of the inhibitors are required in these cases for initiation of DNA replication. Roadblocks formed by termination proteins bound to specific DNA sequences or by persistent RNA-DNA hybrids can also terminate DNA replication. In plasmids replicating by rolling circle, termination of DNA replication is catalized by the nicking-closing activity of the initiator protein at the origin of replication. At this stage a double stranded copy and a single stranded circular intermediate. The nicking-closing activity of the initiator protein at termination can lead to the covalent link to this initiator protein of a small piece of DNA and to the inactivation of this initiator. The single stranded intermediate is converted to a double stranded copy by host replication machinery.

Coupling of DNA replication to the growth of the host cells is a basic strategy that plasmids use to maintain themselves in the hosts. This is achieved by mechanisms that count the number of origins and adjust the average initiation frequency to one per plasmid and per cell cycle. Protein, RNA, DNA and combinations of these are involved in the replication control. Contributions of protein and RNA to this control are relatively well understood. The mechanistic role of DNA sequences in this process, that are instrumental either in regulating the expression of the initiator or in forming protein-ori active/inactive complexes, is the subject of intense research. Phages also control their DNA replication but here the option is, in general, between all (lytic propagation) or nothing (switch-off of the lytic origin and activation of plasmid origin, or passive replication by integration into the chromosome).

The different stages of replication were analyzed in the Workshop using different plasmid and phage systems. Initiation of replication was a focus in these presentations. Much of the functional studies on replication and its control in extra- chromosomal genetic elements involved genetics, biochemistry and physiological analyses. A clear understanding of the macromolecular interactions and mechanisms involved, requires also structural data on initiators, host replication factors, replication control elements and on the macromolecular assemblies involved in DNA replication and its control. From the advanced resolution of some of these structures and the preliminary reports of others, it was clear that the confluence between structure and function is occurring. This will greatly contribute to our understanding of the replication process in prokaryotes. Plasmid and phages appear as a privileged window from which this important scenario could be observed and explored.

This Workshop has been probably the first in which scientists working with these extrachromosomal elements have get together. We were fortunate that the original initiative of this convergence was taken by the Juan March Foundation. On behalf of ourselves, of the two additional organizers, D. Chattoraj and G. Wagner, and of all participants we would like to thank the Juan March Foundation for making possible and very pleasant this highly stimulating Workshop.

Ramón Díaz Orejas and Manuel Espinosa Padrón.

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Mechanisms Involved in Visual Perception

Organized by
J. Cudeiro and A.M. Sillito

(23-25 February)

Questions regarding the nature and the mechanisms of visual perception have provided one of the strongest focuses for multidisciplinary dialogue in the field of neuroscience. The convergence of the interests of philosopher, theoretician, psychophysicist and neurobiologist in vision tracks back a surprisingly long way in time. It has drawn those with interests in the mechanisms of consciousness into a dialogue with those dissecting subtle interactions in elements of neuronal circuitry in retina, thalamus or cortex. The tensions and synergies following from this have provided a potent stimulus to a dialogue that has constantly questioned ways of thinking about visual mechanisms in particular and brain function in general. In setting up this meeting we sought to bring together a selection of those who hold distinctive and nodal positions in the many components of the dialogue that constitutes the current field of vision research.

Advances in our understanding of the retina are providing a growing insight into the nature of the processes which encode the retinal image and drive the central visual mechanisms. The functional specificity of the filters encoding luminance and chromatic signals in primate retina are being linked with increasing confidence to the circuitry and the properties of these filters associated with visual performance in tasks such as vernier acuity. Despite a wealth of evidence to the contrary, there is still an odd tendency to forget that the lateral geniculate nucleus contributes to the visual mechanism and occasionally it seems some may think the retina provides direct input to the cortex. A convergence of anatomical, pharmacological and functional evidence on the other hand shows the presence of a complex, dynamic and potentially very structured influence on the transfer of visual information through the lateral geniculate nucleus. It is cogent to remember that the retinal synapses on relay cells comprise about 7% of the input whilst corticofugal fibres from layer 6 of the visual cortex comprise 30%. The elegant definition of a third visual channel in primates, linked to konicellular type cells in the lateral geniculate nucleus and cytochrome oxidase rich blobs in the visual cortex shows how easily the edifice on which we attempt to formulate our description of the visual system can change. This "K" channel is driven by broad band luminance contrast signals and the blue-on signal from the retina and appears to be strongly linked to the function of the "blobs" in V1.

The complexity and diversity of cortical visual processing does not allow any simple description with hundreds of anatomically defined pathways and at least ten hierarchical stages in the many parallel streams. However, the insight from non-invasive neuroimaging techniques and increasingly sophisticated visual neurophysiological investigations provide an abundance of pointers to organisational detail in both circuitry and processing hierarchies. Once dismissed, shunting inhibition has re-emerged as a mechanism that may play a strong role in the organisation of the receptive field of simple cells in the primary visual cortex. Both models of the circuitry and recent data underline the complexity of behaviour that emerge from multiple interactions in the recurrent and laterally directed networks. The distinction between classical receptive field and surrounding area of visual space blur when the global context of the image shifts the state of the multiple lateral interactions in the successive horizontal networks representing visual space. In visual cortical area MT there is very thought provoking evidence from innovative work suggesting that the organisation of centre and surround mechanisms in neurons provides the basis for a computation representing the direction of surface tilt specified by motion. Interestingly the evolution of the timing of responses to image context such as orientation and motion contrast in the primary visual cortex suggest that these effects may well follow from multiple interactions between different levels in the hierarchy of the central visual system.

Whilst it is easy for the neurobiologist to be caught up by slightly parochial ways of thinking about the mechanisms of visual function the interplay with the many observations on the psychophysics of human visual performance and perception provide a rigour that at the very least generates a sense of caution. The need to avoid "inappropriate concepts or theories that generate imaginary mechanisms" is underlined. Illusions and backward masking provide potent questions to mechanism and increasingly a new repertoire of stimuli to dissect the representation of salience in what seems to be mechanism. Whilst avoiding illusory mechanisms for illusory phenomena we should perhaps also pause before setting anatomical boundaries for the presence and absence of consciousness.

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Notch/Lin-12 Signalling

Organized by
A. Martínez-Arias, J. Modolell and S. Campuzano

(9-11 March)

Co-sponsored by the National Science Foundation (U.S.A.)

The genes Notch from *Drosophila*, and lin-12 and glp-1 from the nematode *Caenorhabditis elegans*, encode single transmembrane proteins which are prototypes of a large family of receptors whose structure and function have been conserved from nematodes to humans. These receptors are basic elements of a signal transduction system which involves ligands and intracellular proteins.

Extensive studies in *Drosophila* and *C. elegans* have laid down a paradigm for the functioning of these receptors. This paradigm is derived from two basic and general observations: first, that the mechanisms which recruit cells for a particular developmental pathway generally select more cells than those that will ultimately follow the pathway; and second that, once some cells have been selected the fate is inhibited in the others. This process is iterative and occurs over and over again in development. Notch is the central element in this decision making process and, in the absence of Notch, cells tend to adopt premature and erroneous fates. As might be expected, constitutive activation of Notch leads to the suppression of cell fates in an indiscriminate manner. The process of cell fate suppression during development is termed "lateral inhibition" and, by regulating the assignment of cell fates, is instrumental for generating pattern.

The conceptual framework derived from studies in invertebrates has been extended to vertebrates. A variety of experimental systems have shown that the notion of Notch as a central element in the process of cell fate assignment is widespread and that ligands as well as signal transducers and, in some cases, nuclear targets of the system are very conserved. A dramatic observation in support of this notion is the association of mutations in Notch with leukemias and other tumours. In these instances the activation of Notch leads to the maintenance of a specific undifferentiated state.

This meeting was convened as a response to the growing realization of the importance that Notch signalling and the processes with which it is associated play in development. It attempts to address many emerging or unanswered questions. For example, the conservation of Notch and of the networks of ligands and, in some cases of transducers, bears the question as to how the pathway is regulated in different biological process and to what extent the lessons from *Drosophila* and *C. elegans* are applicable to vertebrates. In addition, and at a more basic level, there are important questions about the molecular details of Notch signalling that are just beginning to be unraveled. And last, but not least, the association of mutations in Notch with pathological conditions as diverse as cancers and dementia, prompt questions about how general is the picture that is emerging of Notch signalling.

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Membrane Protein Insertion, Folding and Dynamics

Organized by
J.L.R. Arrondo, F.M. Goñi, B. de Kruijff and B.A. Wallace

(30 March/1 April)

Biomembranes have been the object of considerable attention from the point of view of biophysical chemistry for the last three decades. Model membranes consisting of pure lipids were first developed, and integral membrane proteins were later incorporated, or "reconstituted", into lipid bilayers in the seventies. Although much effort was applied in those years to the study of lipid-protein interactions in membranes, these were treated as pre-existing, almost immutable entities. Membrane proteins could be either integral or peripheral; there were as well soluble proteins, unrelated to membranes.

In the last years, however, we are becoming increasingly aware of the dynamic aspects of membrane-protein interactions, in particular in the process of protein insertion into lipid bilayers. From many fields of molecular cell biology we are being confronted with proteins that behave at some stage as "soluble", then, after an appropriate stimulus, they get inserted into the lipid matrix. The question is no longer how lipids and proteins interact in membranes, but rather what is the conformational change that allows the protein to perform the transformation from a water-soluble to a lipid-soluble species, and what is the stimulus that triggers such a change. Other relevant questions include: to what extent do all proteins follow a similar insertion pathway, and what the protein folding mechanisms in aqueous and lipidic environments have in common.

The problem to be dealt with in the workshop had arisen simultaneously in various areas of biology, membrane biogenesis, protein folding, protein toxins and membrane fusion among others. This multiplicity of problems, with great chances of having, at least in part, a common answer, called for a joint reflection by scientists of the various fields involved.

But the problem of membrane insertion, folding and dynamics of proteins is a multi-faceted one also from the methodological point of view: cell physiology and pathology, protein engineering, structural biology and membrane biophysics all have a significant share in the strategy of its unraveling. Though mainly focused on the biophysical aspects, our programme intended to reflect this complexity in the variety of expertises of the invited participants. In turn, this heterogeneity of presentations appeared to be essential for a global, multidisciplinary approach to the subject.

Biophysical, molecular and cellular approaches are being combined in the study of processes that belong to membrane biogenesis, cell physiology or cell pathology. As opposed to the static view of twenty years ago, cell membranes are now seen as dynamic structures, continuously being synthesized in the endoplasmic reticulum, then processed into various organelles following the intracellular "traffic", and finally dismantled in the lysosomes, the whole process being the object of a finely tuned regulation. Intracellular membrane traffic ensures the correct distribution of membranes into the proper organelles, a process that is directly linked to the biosynthesis and insertion of the appropriate proteins in each case. Insertion is now known to be initiated by a combination of "signals" residing in the sequence of the nascent peptide. *In vitro* studies with synthetic peptides have been instrumental in the progress of our knowledge in this field.

Much less is known, unfortunately, of the folding of intramembranous proteins inside the hydrophobic bilayer, in spite of important insights coming out from *in vitro* and model studies, as summarized in the following reports. In particular, the insertion and folding of the large beta-barrels that are found in the various porins are still posing a difficult problem.

In some cases, cell physiology requires the translocation of a protein across a cell membrane. This is the case of some forms of protein secretion, or of mitochondria and chloroplast biogenesis (with some polypeptides being synthesized in the cytoplasm, others being encoded by mitochondrial/chloroplast DNA), or of the periplasmic and outer membrane proteins in gram-negative bacteria. As in other aspects of biology, convergent and divergent evolutionary phenomena appear to coexist, with hints of common patterns being discerned even in apparently dissimilar processes.

Cytotoxicity is another clear example of a phenomenon in cell biology that is conspicuous by the variety of its forms, although some common threads may be uniting many of them. Many phenomena leading ultimately to cell death start with the insertion of a protein in the target cell membrane. This occurs with the lysis of eukaryotic cells by bacterial toxins, either acting at the membrane level or through interference with intracellular mechanisms. But complement-mediated bacterial lysis requires equally the insertion of a complement subunit in the bacterial membrane. Several instances of viral infections and pathogenesis appear as well to be related to an initial event of peptide insertion into a host bilayer.

Not only invited papers but also free communications presented in this Workshop, from a large variety of experimental systems and methodological approaches, contributed to enrich our view of this particular aspect of molecular cell biology, namely the insertion, folding and dynamics of membrane proteins. While many of the questions and enigmas are still to be solved, the Workshop did certainly succeed in reshaping some of our questions and putting certain enigmas under a new perspective.

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Plasmodesmata and Transport of Plant Viruses and Plant Macromolecules

Organized by
F. García-Arenal, K. J. Oparka and P. Palukaitis

(20-22 April)

Everything flows and nothing stays (Heraklitus, 513 B.C.)

Plasmodesmata are symplastic bridges between plant cells that define a topological unit of the plant body, limited by plasma membranes, known as the symplast. Symplastic connection is critical for processes in plant development such as morphogenesis or assimilate transport through the phloem. Thus, plant physiologists and cell biologists have made major efforts to understand the structure and function of plasmodesmata that connect different tissues.

Macromolecules do not pass through plasmodesmata, unless they provide a system that facilitates their own transport. Plant viruses fall into this category. To invade a plant systemically, most plant viruses need to move from the initially infected cells to neighbouring ones, and then, via the vascular tissues, to other parts of the plant. Thus, plant viruses encode proteins that facilitate thier movement through plasmodesmata and into the phloem.

Considerable progress has been made in the last ten years in identifying virus-encoded proteins involved in various aspects of the movement process. These movement proteins have facilitated the understanding of macromolecular trafficking between cells, although less is known about how viruses access the phloem and move within and out of sieve elements. Nevertheless, the various virus movement proteins and viral genetic materials are very useful either as probes or to provide molecular markers to understand both plasmodesmatal functions and processes related to phloem transport.

Consequently the stage has been reached at which there is a convergence between the goals of plant biologists and virologists, with each being able to offer unique contributions and perspectives to the further understanding of the specific mechanisms by which viruses and other macromolecules move within plants. Thus, it was timely that there should be a meeting bringing together these two fields to foster future research and collaboration.

This meeting first reviewed what is known about plasmodesmata structure and development, and then proceeded to consider the progress made in understanding the functions of plasmodesmata through viral and developmental approaches. Processes involved in phloem-dependent transport were examined using different markers such as fluorescent dyes, phloem-specific proteins and viruses. Various viral movement strategies were described, as well as the role of plasmodesmata in the plant's response to pathogen invasion.

The stage is now set for genetic and molecular approaches that will result in the characterisation of the detailed structure of plasmodesmata between different cell types. This will contribute to our understanding of how the plasmodesmal components interact with viral movement proteins and other macromolecules to regulate intercellular communication within plants.

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Cellular Regulatory Mechanisms: Choices, Time and Space

Organized by
S. Moreno and P. Nurse

(11-13 May)

Co-sponsored by the European Molecular Biology Organization

One hundred and sixty years ago Theodor Schleiden and Jacob Schwann proposed the cell theory. This fundamental theory in Biology has two main implications: that every living organism is made out of one or more cells and that cells only arise by the division of pre-existing cells. In the last decade, there has been a lot of progress in our understanding of how cells divide. Most cells must complete four tasks during the cell division cycle. They must grow, replicate their DNA, segregate their chromosomes into two identical sets, and divide. Cell division is controlled by cyclin dependent kinases (CDKs). These protein kinases are periodically activated by their association with cyclins and their activity trigger the different phases of the cell cycle at the right time and in the right sequence. CDK/cyclin activity are themselves regulated by CDK inhibitors, by protein phosphorylation and by protein degradation. The combination of these regulatory mechanisms generate a relatively well characterized biological clock that regulates cell division.

CDK/cyclin complexes induce the onset of downstream events such as DNA replication and mitosis. DNA replication occurs during a short period of the cell cycle called S-phase. At the onset of S-phase, replication origins are activated by CDK/cyclin complexes. Recently there has been a lot of progress in the identification of proteins that bind and regulate replication origin activity. CDK/cyclin complexes also induce the cellular changes required for cells to enter mitosis. In this workshop the molecular details of the initiation of DNA replication, spindle assembly, chromosome movement and sister chromatid separation were discussed.

In multicellular organisms cell division depends on extracellular signals that ensures that a cell divides only when it is required. These signals activate or inhibit the CDK/cyclin complexes leading to cell proliferation or to cell cycle arrest followed by cell differentiation. Some of the cascades induced by these positive and negative signals and their integration with other developmental choices such as cell differentiation and cell death were an important issue of discussion.

In summary, several interesting problems in cell biology were the subject of this workshop. Questions such as: how do biological clocks work? How do cells co-ordinate cell growth with the cell cycle? How do signal transduction pathways stop cell division and induce cell differentiation? How is cell death regulated? How is the spatial organization of the cell recognised during cell division?

S. Moreno and P. Nurse

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Wiring the Brain: Mechanisms that Control the Generation of Neural Specificity

Organized by
R. Gallego and C. S. Goodman

(25-27 May)

We met in Madrid in May of 1998 to discuss how the brain gets wired up. Specificity in nervous system wiring unfolds in a series of overlapping developmental steps. Neuronal growth cones navigate specific pathways and choice points. They find and recognize their correct targets and make initial patterns of stereotyped synaptic connections. The pattern and strength of these synapses is then refined, remodeled, and adjusted during development, a process that continues throughout life. Our Workshop reviewed progress in all of these areas, including the discovery of molecules, the elucidation of mechanisms, and the overall sophistication with which the field now approaches these questions.

A common coffee break topic was to marvel at just how far the field has come since we last met five years ago in Cuenca in 1993. Cuenca represented a transition from the cellular level of analysis of the 1980's as we ushered in the molecular genetic analysis of the 1990's. During the 1980's, specificity was defined, simple model systems explored, and a diversity of molecules and mechanisms implicated. It was a decade of clever *in vivo* and *in vitro* manipulations, from transplants and ablations to stripes and collagen gel assays. Elegant stories emerged concerning the development of motoneuron projections, retinotectal topography, other sensory projections, projections to and from the cortex, spinal cord wiring, and a variety of axon projections in flies and worms. We came to realize that repulsion is just as important as attraction, that guidance cues can work at long-range as well as short-range, and that guidance and connectivity are based on more than differential cell adhesion.

The either/or arguments of activity-independence vs. activity-dependence gave way to a perspective in which both mechanisms work in concert to construct the nervous system. Beautiful examples emerged showing just what activity does and does not normally do in patterning and refining connections. In short, during the 1980's, the dust settled on some of the old arguments in the field, and we got down to the hard work of trying to discover how nervous systems are actually constructed. As the 1990's approached, a variety of laboratories headed off in search of guidance and connectivity molecules, some using *in vitro* assays and biochemical approaches, while others took an *in vivo* genetic approach. Other laboratories used imaging and biophysical methods to further explore the mechanisms and roles of patterned activity.

What emerged at Cuenca in 1993 was that all of these approaches were beginning to pay off with great success. We heard about the discoveries of a variety of new IgCAMs and other cell adhesion molecules. Having heard for over a decade about what CAMs might be capable of doing, we finally started to hear what they actually do in the developing organism. We heard the further details of many different repulsion assays, and the characterization of a variety of activities and factors. The structure of the first growth cone collapse molecule -- Collapsin in chick -- was announced, and it was shown to be highly related to a recently described and otherwise novel guidance molecule -- Fasciclin IV in grasshopper. Related molecules were known in flies, and were just being discovered in humans. Within a few months, papers were published suggesting that both of these proteins were members of a broader family of molecules, called the Semaphorins, that were conserved across phylogeny. In the wind was the ongoing purification of the floor plate factor, which emerged one year later as the discovery of the Netrins, and their homology to UNC-6 in nematode. The genetic analysis in worms, with the interactions of *unc-6* with *unc-5* and *unc-40*, suggested candidate receptors for the Netrins in mammals. That too would

emerge between Cuenca and Madrid. Topography was still in search of its first molecules -- the relevance of the Ephrins and Eph receptors in this process were still a few years off. On the activity front, the first signs were starting to emerge that not all neurotrophins were functionally identical to NGF, and that some might do more than simply control cell survival.

What has happened since Cuenca?. It was striking in Madrid in 1998 to see the ways in which our field has grown up, dug in, and begun to explore molecular mechanisms in a deeper and more biologically meaningful fashion. The field's assays and approaches have shifted towards more relevant ones. In the early 1990's, the dominant *in vitro* assays were based on simple neurite outgrowth; by 1998, many labs seemed to be using more relevant assays that provided choice and context, including both stripe and collagen gel matrix assays, and the use of transfected cells producing defined molecules. On the *in vivo* front, more people were using genetic or other molecular perturbations. Conditional genetic manipulations were just beginning to infiltrate our field.

In 1993 we knew that guidance could either be attractive or repulsive. By 1998 we had realized that most guidance decisions were not either one or the other, and were not based on a single molecule or mechanism, but rather that at most choice points, growth cones measure the relative balance of attractive and repulsive forces and respond accordingly. Names such as Netrins, Semaphorins, and Ephrins, and some of their receptors were household words that no longer needed introduction. At the same time, some new molecules emerged -- for example, the Slits and Robos. And intriguing transgenic results compelled us to consider that olfactory receptors led a double life in vertebrates, playing a role in guidance prior to their role in smell.

One theme of the meeting was the notion that changes in growth cone responsiveness are an important feature of the dynamic nature of guidance decisions. Growth cones *in vivo* can change their guidance receptors (either the levels or functions of these receptors) and thereby their responsiveness; *in vitro*, changes in second messenger systems and other associated proteins were shown to lead to dramatic changes in responsiveness. Some molecules that we thought functioned in repulsion can also function in attraction, and some that we thought were involved only in attraction can also function in repulsion. Detailed analysis in a number of well-known model systems, from the midline to motoneurons and from retinal to olfactory topography, showed us that guidance and targeting are not built with the principle one molecule/one choice or one molecule/one synapse. Knock-outs and knock-ins showed fascinating phenotypes, but rarely the simplest growth cone behaviors that would be predicted if single molecules controlled single guidance or connectivity decisions. Other systems, such as cortical and hippocampal connections, are just beginning to be explored, and appear to use many of these same molecules and principles.

In 1993, we heard about the first wave of new molecules, whereas in 1998 we heard about more members of those gene families, and some new gene families as well. The next frontier is integration and signal transduction, that is, dissecting how growth cones decipher and integrate all of the conflicting signals impinging on them, and translate them into meaningful guidance decisions. In 1998, a genetic analysis in Drosophila gave us our first glimpse of how guidance receptors might hook into local actin polymerization and depolymerization via adapter proteins (such as Dock) and small GTPases (such as cdc42). Five years from now, we'll no doubt have shed our innocence and joined the rest of cell biology in the morass of intersecting and intertwined signaling systems, hoping to understand how growth cones make decisions.

Synapse formation continues to be most elegantly dissected, in terms of cellular mechanisms and manipulations, at the neuromuscular junction. Although we know a great deal about the molecules that control receptor localization and gene expression, we are still in search of molecular mechanisms that control who wins and who loses during the process of synaptic refinement. One of the neurotrophins, BDNF, was shown to play an essential role in one form of synaptic plasticity in the adult, although it is still unknown how this and presumably other molecules control the developmental remodeling of synapses.

One principle that emerged in 1998 was the remarkable degree to which a variety of circuits generate their own bursting activity during development. First seen in the form of the retinal waves, and now extended to brain circuits throughout the visual pathway, such phenomena were shown for motoneurons in the spinal cord as well. Moreover, these patterns of electrical activity in the embryo have their own special biophysical and neurochemical properties that point to them being a unique and transient mechanism. We heard of the first successes using molecular methods to discover genes whose expression is turned on by activity. One of these activity-dependent genes, *MHC*, is particularly intriguing given how it functions in the immune system.

Interestingly, the temporal separation of activity-independent and activity-dependent mechanisms became further blurred. First the field learned that activity is likely to control synaptic growth and retraction by calling forth the same sorts of molecular mechanisms that function during activity-independent phases of development. Moreover, a beautiful example was described in which activity was shown to be necessary for an otherwise activity-independent process of axon defasciculation and selective refasciculation of motor axons.

Where will we be in 2003 when our community meets again for its 5 year progress report? Obviously, we'll have more molecules and a deeper understanding of mechanisms, particularly in terms of signal transduction, cytoskeletal changes, gene expression, and cell-cell interactions. We might even know (perhaps not in the full biblical sense, but nevertheless at some textbook level) how some guidance and connectivity decisions are made in the organism. But no doubt, we will see some additional transitions in our thinking and analysis, some predictable, and others not. For example, whereas the 1990's will have been the decade in which we embraced the remarkable conservation in gene structure and function across species, the next decade is likely to see us focus on the differences. The evolution of behavior must have its roots in specific changes in circuitry, and such differences in connectivity must have their basis in changes in the expression of guidance and connectivity molecules. Having learned that all organisms use the same molecules and mechanisms for wiring (and having exploited this conservation to learn how they function), the next challenge will be to discover how subtle differences in the expression of these molecules controls the evolution of brain and behavior.

Corey S. Goodman and Roberto Gallego

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Bacterial Transcription Factors Involved in Global Regulation

Organized by
M. Vicente, A. Ishihama and R. Kolter

(11-13 June)

Despite their constrained dimensions, microbes are very successful life forms, able to colonise the most extreme environments. Microbial cells, when compared to the eukaryotic ones, contain very simple structures. Some microbes (*Mycoplasma*) may cope with life with just 1% the quantity of genes that a human cell needs to carry. As the structure of the bacterial genes is relatively simple - without introns or other adornments - the economy in genetic material is even more remarkable: one human cell contains more DNA than one thousand *Escherichia coli* cells. Their limited amount of genetic information is nevertheless managed by microbes in an exquisite manner, exploiting all imaginable devices both at the molecular, physiological, and cellular levels to attain their primary goal: survival and proliferation. The basic mechanisms used by microbial cells to manage their small and compact genetic information involve, nevertheless, similar principles as those found in their eukaryotic counterparts.

Although *E. coli* contains 4288 potential genes (some 30% with unassigned function), the number of RNA polymerase molecules per cell is calculated to be limited to 2000. This paucity in the amount of transcriptional enzyme is managed by the regulatory networks of the bacterial cell in a very efficient manner. Bacteria can respond to a diversity of stimuli and stresses by wisely regulating the molecular mechanisms involved in transcription. At least one third of the molecules in the polymerase core enzyme population are not engaged in transcription, forming a pool that can be called into action in response to environmental changes. Free core RNA polymerase molecules can be directed to transcribe specific regulons by association to an assortment of alternative sigma factors (at least seven in *E. coli*) which are themselves expressed under specific circumstances. If required, the cell can specifically inactivate some of its sigma factors by complementary anti-sigmas.

A set of nearly one hundred transcription factors can modify the expression of specific genes by establishing intermolecular contacts with DNA and the different subunits of RNA polymerase. In addition to the dedicated transcription factors, members of the class of DNA-binding proteins (IHF, Fis, HU, HNS...) are known to contribute to transcription regulation by modifying the architecture of many regulatory regions, bringing together in three dimensional space DNA sequences that may be not so near each other.

The expression of genes controlling functions essential for cell proliferation involves a high complexity, beginning with the number of promoters implicated. Even bacteriophages use to their advantage many of the molecular subtleties present in bacterial cells to fine tune the expression of relevant genes to the specific needs of the different stages in their lytic cycle. Their case can be considered as a rudimentary stage of differentiation, which in those bacteria that undergo differentiation (*e.g. Caulobacter crescentus*) is achieved, as it is in eukaryotic cells, by sequentially turning on and off some genes, and by compartmentalization.

Survival is one of the goals of bacteria, and it involves processes in which they have been peculiarly inventive. Under adverse circumstances *Bacillus subtilis* cells undergo sporulation. The production of a spore is the result of different sigma factors being selectively activated and sequestered into different compartments, what results in the activation of specific genes. Even cells of *E. coli*, which do not sporulate, are not dull in their demise. Entrance into stationary phase triggers the expression of specific genes directed by the appearance of a specific sigma factor, σ^S, and the inhibition of σ^D, the "housekeeper" sigma which transcribes most of the promoters during exponential growth, by an anti-sigma.

It is within this perspective that bacterial gene expression is viewed in recent times as a rather elaborate web of interactions, comprising various regulatory circuits controlled by an assortment of molecules. The relative simplicity of the *lac* operon served in the past as a model to stimulate research in Molecular Genetics, but it may no longer be considered as the paradigm of the bacterial expression unit. When studied at the global level, the complexity of bacterial regulatory mechanisms may serve to stress that the complexity of eukaryotic cells is not unique in the phylogenetic scale.

The description of the molecules involved in the initiation of transcription, in modifying the architecture of DNA, and monitoring the global state of the cell comprised the first part of the Workshop on "*Bacterial Transcription Factors Involved in Global Regulation*". How these mechanisms operate at the cellular level during the growth and survival of bacterial populations was discussed in the second part. The workshop finished with descriptions of the regulatory circuits operating during cell division, differentiation and sporulation.

Miguel Vicente, Roberto Kolter and Akira Ishihama

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Nitric Oxide: From Discovery to the Clinic

Organized by
S. Lamas and S. Moncada

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Nitric oxide, discovered in biological systems a little over a decade ago, continues to arouse intense interest among the community of life scientists. Not only can this biological mediator convey crucial signals which result in a wide spectrum of effects (vasodilatation, modulation of neurotransmission, host defense in the immune response), but also it is now clear that it may act as an important regulator of general cellular processes such as gene expression and mitochondrial function.

NO is synthesized from the amino acid L-arginine through the action of a family of enzymes termed nitric oxide synthases (NOSs). Three main isoforms have been identified, two constitutive (nNOS and eNOS) and one inducible (iNOS), all sharing common functional and structural features. Two main domains may be distinguished in the NOSs: an N-terminal oxygenase domain and a reductase domain, the latter highly resembling cytochrome P-450 reductase. The three-dimensional structure of the oxygenase domain from two of these isoforms (iNOS and eNOS) has recently been determined, providing important insight into structure-function relationships of the dimeric proteins and revealing the potential interaction between substrate and allosteric modulators within the oxygenase domain. Each isoform has a particular mode of regulation: while iNOS is mainly regulated at the level of transcription, nNOS and eNOS are regulated through posttranslational modifications and protein-protein interactions. In endothelial cells as well as in cardiac myocytes, eNOS myristoylation and palmitoylation serve to target the enzyme to the particulate subcellular fraction, where eNOS is localized in plasmalemmal caveolae. These are specialized cholesterol-rich invaginations of the plasma membrane, which associate with several signalling proteins. A structural protein of caveolae, caveolin, inhibits eNOS enzyme activity, and the inhibitory eNOS-caveolin complex is reversibly disrupted by calcium-calmodulin in a regulatory cycle modulated by G protein-coupled receptors.

The so-called "constitutive" enzymes, eNOS and nNOS, can be transcriptionally or posttranscriptionally regulated by a variety of stimuli. Hypoxia, shear-stress and estrogens are among the stimuli capable of modulating eNOS mRNA and/or protein levels. Cyclosporin A (CsA), a calcineurin-inhibiting immunosuppresor, upregulates eNOS mRNA expression in endothelial cells by transcriptionally-dependent mechanisms. The protective role of NO against atherosclerosis can be improved by estradiol which, at physiological concentrations, increases eNOS expression *in vivo*.

Pharmacological approaches to the study of the functions of NO have classically used NOS inhibitors, as well as NO donors. In recent years, alternative approaches are emerging which make use of genetic tools. Knockout mice for nNOS have unveiled the participation of this enzyme in the development of neurotoxicity after cerebral ischemia and in the motility of the gastrointestinal tract. Studies in eNOS knockout mice are consistent with a protective role of eNOS against increased intimal proliferation following vessel injury. This has significant implications in atherosclerosis and makes eNOS an important target for gene therapy to restore endothelial generation of NO.

NO has long been recognized as a modulator of the immune response as it may behave as a regulator of the balance between Th1 and Th2 responses in the immune system. In iNOS-deficient mice there is a predominance of the Th1 response, as evidenced by an increased production of IL-12 and IFN-γ and decreased IL-4. In contrast, high amounts of NO down-regulate the generation of IL-12, thus reducing the Th1 response. The role of NO on gene expression in cells treated with pro-inflammatory stimuli appears to be controversial, since both positive and negative effects of NO have been encountered. Nitric oxide has been reported either to protect cells from apoptosis or to cause apoptotic cell death depending on the target cells, the local concentration, and the relative amounts of other reactive species.

In the nervous system, NO has been implicated in numerous phenomena ranging from the acute regulation of neural function to the long term regulation of synaptic efficacy. Clearly cGMP is an important mediator of NO actions in the nervous system. However, after prolonged NMDA receptor stimulation, NO may be produced in excess and become toxic to neurons through mechanisms that appear to be cGMP-independent. NO may play also a role in ischemia-reperfusion neurotoxicity. Nitric oxide may modulate sensory-motor processing such as eye movement and also play important roles in the regulation of gastric function by acting on the central nervous system.

When analyzing studies with NO donors several factors should be considered. Among the most critical are the diversity of the pharmacological tools employed as donors of NO and the highly variable rate of NO release by these compounds. Besides, it is possible that, in addition to NO, some of these substances favour the synthesis of other reactive intermediates. Among these is peroxynitrite ($ONOO^-$), a highly toxic and reactive radical, which interferes with signal transduction pathways and structural proteins by promoting the nitration of tyrosine residues. Genes conferring resistance to reactive nitrogen intermediates (RNI) have been recently characterized in *M.tuberculosis* and other species. One of these, encoding for alkylhydroperoxide reductase subunit C, seems to be the most widely distributed gene protecting cells directly from RNI and provides the first known enzymatic defense against an effective element of anti-tubercular immunity.

Long term exposure to NO irreversibly inhibits mitochondrial complex I under conditions of low glutathione concentration. This inhibition may result from S-nitrosylation of critical thiols in the enzyme complex since it can be reversed by exposing cells to high intensity light or by replenishment of intracellular reduced glutathione. Thus, although NO may regulate cell respiration physiologically by its action on complex IV, prolonged exposure to NO leads to persistent inhibition of complex I and potentially to cell toxicity.

Important progress has been made in the area of NO and human pathophysiology. Reduced NO-mediated dilatation has been reported in patients with cardiovascular disorders including hypertension, diabetes and hypercholesterolemia. Although levels of NO are increased in hypotensive patients with septic shock and a NOS inhibitor, L-NMMA, may restore blood pressure, the mechanisms by which infection might alter NO generation and vascular response in humans are complex and await further research. NO has been shown to inhibit cell proliferation. However, the mechanisms by which this effect takes place are still obscure and seem to be cGMP-independent, at least in part. N-hydroxyarginine , an intermediate in the NO synthesis pathway, might account for the antitumoral effects observed in a human colon carcinoma cell line. It is also possible that the inhibitory actions of NO on cell proliferation are mediated by the inhibition of ornithine decarboxylase.

NO is progressively being incorporated as a therapeutic tool. Inhaled NO is an effective therapy in neonates with pulmonary hypertension and patients with acute respiratory distress syndrome. Very recently, and through yet undetermined mechanisms, NO has been shown to improve sickling crises in patients with sickle cell anemia.

In summary, NO continues to be a fascinating biological mediator for which new biochemical roles, physiological functions and therapeutic applications are being unravelled day by day. This workshop showed that standardization of experimental design and of the use of NO donors as well as criteria for their employment are now necessary for valid interpretation of the huge amount of literature published in this field. As usual, the Centre for International Workshops in Biology at the Fundación Juan March provided the perfect environment to foster scientific discussion, exchange of ideas and social interaction.

Santiago Lamas and Salvador Moncada

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Chromatin and DNA Modification: Plant Gene Expression and Silencing

Organized by
M.A. Vega-Palas, T.C. Hall, A.P. Wolffe and R.F. Ferl

(5-7 October)

Alan Wolffe likes to quote from a review which claims "chromatin is the last refuge of scoundrels". From this workshop, it appears that the number of scoundrels is increasing and that they are no longer seeking refuge!

Although it has long been recognized that transcriptionally active domains of chromatin are relatively highly acetylated, the identification of multiple histone acetyl transferases (HATs) and histone deacetylases (HDs) capable of modifying specific lysine residues in specific genes is very recent. Acetylation of lysine residues in the N-tails of core histones is now seen as loosening the chromatin structure thereby permitting access by transcription factors and potentiating a gene sequence for transcriptional activation. Conversely, methylation of both DNA and histones is now recognized to permit recruitment of proteins such as MeCP2 that condense chromatin, leading to transcriptionally inactive domains. The latter interactions are highly parallel to the inactivation of transgenes, specially in plants, that falls under the general term "gene silencing".

Fundamental insight to nucleosome packing and transcriptional activation has been gained through studies in animal models such as MMTV, and information concerning the relationship of chromatin modification and gene function is now growing for plants, especially through the study of transgenes. This workshop provided an unprecedented opportunity for the exchange of information between animal and plant scientists who are focusing on the relationship of chromatin to transcriptional activation and inactivation, and the outcome will be stimulating to research in both fields.

The presentations first explored chemical modifications of chromatin such as acetylation, methylation and phosphorylation. From the work discussed, it became apparent that parallel situations exist for animal, lower eukaryote and plant systems, with regulatory systems balancing HAT and HD activities for specific genes during development. Methylation of chromatin generally represses expression, and probably reflects genome defense systems that may be ancient in origin and retained to suppress the activity of retroviral elements that are now known to be ubiquitous and abundant in eukaryotes from maize to man. In addition to their original functions, these active defense mechanisms appear to be effective in silencing transgene sequences that are recognized as intrusive to the genome. Methylation may be signaled by sequence duplication and can probably act through various pathways to achieve transcriptional inactivation.

Examples of two step processes in gene function - potentiation and transcriptional activation - were provided for both animal and plant systems that are known to have precisely positioned nucleosomes. While acetylation is clearly a powerful force in potentiating a chromatin domain for activation, alternative or interactive systems such as the ATP-dependent remodeling of nucleosomes by SWI/SNF complexes is now well established and exciting information describing the interaction of such remodeling machines with nucleosome arrays was presented. It seems that for several gene systems we are drawing close to an understanding of the mechanisms that trigger the cascade of events involved in transcriptional activation.

New work predicting a highly compacted, interdigitated helical model for chromatin and contemplation of the potential role of DNA topology in setting chromatin structure suggested that much remains to be learned in the area of chromatin. It was also evident that features of higher order chromatin structure, such as the matrix attachment regions (MARs) need further evaluation as to their potential role for diminishing the effect of chromosomal location on activity. Especially important work was described relating transgene position, located by fluorescent in situ hybridization, with function. At an even higher level of organization, the existence of ordered chromosomal arrays in cells and even of mobile RNA arrays (coiled bodies) within the nucleus reminded us that many new treasures are likely to be found in the Pandora's Box that we know as the eukaryotic cell.

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Transcription Factors in Lymphocyte Development and Function

Organized by
J.M. Redondo, P.D. Matthias and S. Pettersson

(19-21 October)

During the last 6-8 years there has been a rapid expansion in our understanding of the molecular mechanisms underlying the regulation of gene transcription, signal transduction cascades and developmental programs in mammals. In particular, the hematopoietic system typified by the lymphoid system has established itself as the foremost paradigm for the study of cell-specific transcription and signal transduction in a physiological setting. In addition, many of the findings have led to new insights into the developmental cues that guide the development as well as execute the effector functions of the immune system. The two arms of this system, the T and B lymphocytes, share many common regulatory mechanisms and also have some notable differences. To properly function, the immune system requires an intimate interplay between these two cell types. Therefore, the idea to organize a workshop that would bring together scientists working on transcription control and signal transduction in B and T lymphocytes made perfect sense, as was evidenced during the course of the meeting.

The contributions presented in the workshop highlighted the major role that transcription factors play in controlling the development and homeostasis of the immune system. Thus, many of the specific functions of transcription factors as regulators of hematopoietic development at early and late stages, in lymphocyte differentiation processes, or as integrators coupling extracellular stimuli to gene expression programs (lymphoid cell maturation, differentiation, activation etc.) were presented and discussed. Many of the experimental approaches were based on the generation of knockout mice lacking transcription factor genes or transgenic mice overexpressing them. The results presented evidenced the critical involvement of different transcription factors in T and B lineage development, lymphoid-cell differentiation as well as the multiple biological functions needed to maintain the regulatory and effector functions of the immune system. Similar strategies using transgenic and knockout mice expressing or lacking signal transduction components allowed the identification of signalling cascades and kinases regulating T cell development. Also, experiments using mice harbouring miniloci transgenes comprising the enhancers of B or T cell-specific genes revealed the role of these cis-acting elements in the tight temporal and spatial regulation of recombination and cell-type specific gene expression.

These results also introduced chromatin as an important component in the regulation of complex developmental pathways. Besides these analyses using mice models, a number of talks of the workshop established functional connections between transcription factor activity and the regulation of differentiation and function of lymphocytes using in vitro models. Thus, several contributions were concerned with the analysis of the molecular mechanisms by which transcription factors may regulate cell cycle control, proliferation or apoptosis in lymphocytes. Similarly, work on the role of signalling cascades connecting extracellular stimuli with transcription factor activation (or deactivation) and the subsequent effects on lymphoid gene expression was also presented.

This workshop gathered scientists working on transcription in the B and T cell fields, and provided a unique and exciting forum to exchange, discuss, and integrate the most recent information on lymphocyte development and function, critical issues for a better understanding of the function and regulation of the immune system.

J. M. Redondo, P. Matthias and S. Pettersson

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Novel Approaches to Study Plant Growth Factors

Organized by
A.F. Tiburcio and J. Schell

(16-18 November)

Plant hormones are the biochemical messengers translating the genetic blueprint of plants into their fully developed, final form. Traditionally, they were grouped as: auxin, cytokinins, gibberellins, ethylene and abscisic acid. However, it is becoming increasingly clear that the classic phytohormones may not be the only molecules involved in the control of plant growth and development. Thus, it is now accepted that a variety of novel signal molecules, such as polyamines, brassinosteroids, jasmonates, salicylic acid, oligosacharides and most recently peptide growth factors, can play a crucial role as signals in the development either participating in the action of, or supplementing traditional phytohormones.

The mechanism(s) by which plant hormones and growth factors trigger physiological processes has been a very difficult question to approach. The advent of modern molecular biology and molecular genetics has revolutionised our ability to unravel the complexities of plant hormone signal action in general, as well as helped to define novel forms of biochemical signalling in plants. Different approaches are now available, each technique having its own strength and limitations. The researcher, therefore, must carefully select the technique(s) to be used according to the question(s) that she or he would like to answer.

Molecular cloning has identified a number of genes that respond to several plant hormones as well as genes involved in the biosynthesis and the metabolism of plant hormones. Promoter analysis of hormone regulated genes has lead to the identification of cis acting elements that control the expression of those genes. Progress has also been made in identifying some of the specific trans-acting factors that interact with such promoters. With the availability of some of the key genes involved in the biosynthetic pathways, it has become possible to manipulate hormone levels using antisense and sense transgenic approaches. This technology eliminates or greatly reduces problems associated with uptake, transport and metabolism of exogenous applied compounds. By using tissue specific or inducible promoters it is also possible to direct hormone alterations to specific tissues or to induce hormonal changes at specific developmental stages. Transgenic plants have proved valuable not only for the study of hormone biosynthesis and action, but also from an agronomic point of view. The work with delayed ripening tomatoes is one of the most advanced examples of a practical application of hormone manipulation in transgenic plants. However, this technology has its limitations since some unexpected results have also been obtained.

The genetic approach has also led to significant advances in several areas of plant hormone biology. The availability of hormone-insensitive mutant plant-gene libraries will likely encompass and allow us to identify hormone receptors, critical components of the signal transduction pathway, and possibly elements involved in uptake and/or metabolism of the hormone to an active form. The screening of mutant plant libraries created by radiation, chemical, transposon or T-DNA tagging techniques has led to the identification of a number of genes implicated in hormone signal transduction as well as to the cloning of some hormone receptors, like the ethylene ETR-1 receptor. The problem usually resides with the nature of the screen used to identify novel signalling genes. In this regard, the use of the green fluorescent protein (GFP) fused to hormone-regulated genes may allow the screening of large numbers of plants simply by looking for the presence or absence of fluorescence. Novel techniques such as differential display and amplified fragment length polymorphism (AFLP) in combination with GFP promoter fusion expression in mutant libraries could provide a powerful means of identifying signal transduction genes. However, the genetic

approach also has limitations: some genes may act at more than one stage in development and growth, or may function in more than one cell or tissue type, making phenotypic analysis difficult. For example, the identification of a cyclic ADP-ribose in abscisic acid signalling through microinjection experiments might not have been possible with a traditional genetic screen.

A number of plant signalling genes have been cloned by mutant complementation in yeast. The real power of yeast is the abundance of mutant strains in which specific signalling pathways have been knocked out. Consequently, genes may be cloned in these mutants by their ability to restore function to the mutant. In addition to complementation, a technique known as the two-hybrid system can also be used. This system can be used to identify new proteins that bind to a protein that has previously been identified within a signal transduction pathway. Hormone signalling pathways in plants may thus start to be delineated by using these techniques.

This workshop brought together scientist actively engaged in plant hormone signalling using molecular and genetic approaches. The workshop was very fruitful and 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.

J. Schell and A. F. Tiburcio

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Structure and Mechanisms of Ion Channels

Organized by
J. Lerma, N. Unwin and R. MacKinnon

(30 November/2 December)

We met in November 1998 to discuss how ion channels are designed and work. Most meetings on ion channels over the last ten years or so have centred around biophysical measurements at the single molecule level and site-directed mutagenesis experiments combined with electrophysiological study of function. And powerful though these techniques may be, the amount of clear-cut information obtained is limited compared with the amount we can learn from viewing three-dimensional structures directly. What set this channel meeting apart from the previous ones is that there was a shift in focus, with structure obviously taking centre stage. Indeed, the meeting seemed to portend a new era of ion channel investigation in which we will be obtaining fresh insights simply by examining the new three-dimensional structures and relating their specific features to their specific functional roles.

Ion channels are integral membrane proteins. Their transmembrane character, and the fact that cells do not in general make many channels, have in the past represented obstacles too severe for any structures to be solved. But several strategies have been developed successfully over the last few years to circumvent the problems of hydrophobicity and availability in small quantities. One is to work with bacterial homologues of the usually more complex eukaryotic protein, and make use of bacterial expression to obtain the large amounts of protein required for crystallisation trials and eventual X-ray structure determination. It was this approach that led to our first high resolution picture of an ion channel, the K^+-selective ion channel of *Streptomyces lividans*, and next, to the structure of the pentameric mechanosensitive channel from *Mycobacterium tuberculosis*. Another strategy has been to engineer soluble parts of the channel protein, which are more tractable experimentally, and gain from them valuable information about critical functional regions. The crystal structures of the ligand-binding core of the glutamate receptor, the cytoplasmic tetramerisation domain of the voltage-gated K^+ channel and an amino-terminal part of the Herg K^+ channel provide elegant examples based on this approach. A third strategy has been to determine the whole structures by electron microscopy of frozen crystalline sheets or tubes, taking advantage of the propensity of channels to organize in two-dimensions – as in the lipid bilayer – rather than three. Resolutions approaching the atomic level are now being obtained from aquaporin and the nicotinic ACh receptor by this means.

Many of us marvelled not only at the rapid progress made over the last two years, but also at the diversity of structures invented by Nature to transport ions (and small molecules) rapidly and selectively across the membrane. The FhuA protein somehow makes use of a globular plug, enveloped by a β–barrel, to translocate ferric ions across the membrane; the homologous Ca^{2+}– and H^+– ATPases each use ten membrane-spanning α-helical segments, arranged in a complex bundle, to pump their respective ions across the membrane; aquaporin is a tetramer in which each subunit makes a transmembrane pore, lined by hydrophobic and polar side-chains, specifically for water molecules to pass through; gramicidin is a helical dimer extending across the bilayer, in which the carbonyl groups of the polypeptide backbone, rather than the side-chains, face inwards creating a central cation-selective pore; the gap junction channel is a hexamer of protein subunits, each essentially a four-helical bundle, delineating a central non-specific pathway for the ions.

Several basic principles underlying the structure and operation of ion channels were illuminated beautifully at the meeting through the details of the structures which have just been determined. In the case of the K^+ channel, for example, the K^+ selectivity over Na^+ is explained by the presence along the 4-fold axis of a 12Å long filter lined by backbone carbonyl groups which are

geometrically constrained so that a dehydrated K^+ ion fits with good coordination but a Na^+ ion is too small. Also in this structure, helix dipoles and a water-filled cavity overcome the electrostatic energy barrier facing an ion in the membrane interior; on the other hand, such features are not apparent in the aquaporin pore, which is designed to prevent the transport of ions – i.e. destabilize their presence in the membrane interior – and only let water molecules through.

Another major theme of the meeting was the molecular mechanisms of ion channels: we ultimately need to understand how ion channels are regulated by ligand-binding and/or by changes in membrane potential. Essential insight into these processes is now emerging from several kinds of biophysical technique. Site-directed spin labelling and EPR spectroscopy is shedding light on the nature of the structural rearrangements underlying gating of the K^+ channel. Small-angle X-ray scattering is telling us about the conformational changes that take place on the binding of glutamate to the glutamate receptor ligand-binding domain. Combined mutational and electrophysiological studies are providing valuable new information about the conformational changes and the subunit interactions involved in a number of channel types, including K^+ channels, cyclic nucleotide-gated channels, glutamate and NMDA receptors. And finally, experiments done on kainate receptors emphasise the importance of functional studies, which link channel mechanisms with other cellular processes and place channels properly in the context of the living organism.

This meeting involved only a small group of individuals. But the amount of fundamental new information presented in the talks and the posters, and also the excitement and discussion they inspired, was amazing. Substantial advances are taking place now in the ion channel field. We can realistically look forward to viewing in the near future several more ion channel structures. Some of these might reveal more complex (and unsuspected) architectures and others might illuminate structural principles underlying the physiological events. What is certain is that all will deepen significantly our understanding of how ion channels are designed and work.

N. Unwin, J. Lerma and R. MacKinnon

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Protein Folding

Organized by
M. Rico, A.R. Fersht and L. Serrano

(14-16 December)

The information encoded in the genome of any living system has to be translated into protein sequences in order to generate biological activity. Protein molecules are synthesized in the ribosomes as linear polypeptide chains, which must fold into their well-defined three dimensional structure in order to be functionally active. Understanding how this functional three-dimensional structure is obtained is one of the fundamental problems still to be solved in modern Biochemistry. Much remains to be known about the forces involved in determining protein folding and stability. Yet the problem is important not just from an academic perspective but from a practical point of view. There is for instance a growing pressure to solve it in order to fill the gap between the number of known sequences provided by the different genome projects, and the number of known structures determined by NMR and X-ray crystallography. Rational proposals for the obtention of, *i.e.*, novel proteins with improved or new biological activities can only be made on the basis of the three-dimensional structure, which for heterologous proteins cannot be predicted from the aminoacid sequence up to the present time. The same can be said for proteins which can be considered as drug receptors, so that folding is also a central issue in drug discovery for use with pharmaceutical and medical purposes. More recently, there is a growing evidence that folding is coupled intimately with the localization and regulation of biological activity. Misfolding events therefore lead to malfunctioning of living systems, and an increasing range of diseases from cystic fibrosis to Creutzfold-Jakob disease and Alzheimer's is now associated with such problems.

During the past few years, recent advances in both experimental and theoretical aspects have offered new insights into the basis of the problem. The aim of the Workshop was to provide a forum for discussion on recent advances and methodological developments in protein folding on the part of leading experts in the field. The Workshop was directed to a wide range of scientists, more or less connected to this important biological problem, and the main intention was to enrich their views on those aspects less familiar to them.

The developing of very simple theoretical models that can reproduce some of the experimental results obtained with real proteins, the so-called lattice models, have captured the imagination of many people in the protein field. These approximations provide some microscopic insight into the process of protein folding and could help in the interpretation and design of future experiments. A long term goal in protein folding is to predict the pathway of folding of proteins by computer simulation. Recent Molecular Dynamics simulations from several laboratories are showing that the goal can be accomplished for the unfolding of small proteins as demonstrated by the good agreement obtained between the predicted pathways with the experimental results coming out from protein engineering studies.

Simple experimental protein systems have shown to be invaluable in obtaining meaningful data about the main factors involved in the folding process. We are approaching a moment in which due to the number of experimental models analyzed, there is enough information to start proposing unified models explaining the folding reaction of small proteins. In particular the development of methods that allow the monitoring of folding stages in the μs range, have provided for the first time insight into the early folding events. Similarly recent advances in NMR and Mass Spectroscopy have allowed us to monitor specific conformations in the denatured state, as well as of the progression of the conformational ensemble to the folded state.

While still we are far from understanding the folding process and from predicting correctly the 3-D structure of a particular sequence, several groups have started to use the information already available to design new proteins. The *de novo* design of proteins implies the possibility of rationally modifying existing proteins, or the design of sequences that should adopt a given target fold. During the past five years this field is coming into a mature state as demonstrated by the results presented in the Workshop, according to which many different successful rational designs have been accomplished. The possibility of increasing the stability, selectivity or catalytic efficiency of a protein has then proven to be possible.

In the last few years a large number of proteins that assist protein folding *in vivo* (chaperones) have been discovered. Some of them have been shown to be highly versatile chaperones since their assistance range from folding of nascent proteins to proteolytic degradation of unstable proteins. While most proteins appear to fold upon release from those chaperones, certain slow-folding and aggregation-sensitive polypeptides seem to be subsequently transferred to a cylindrical protein complex (chaperonin) for folding in the sequestrated environment of its central cavity. Questions related to this important and new field of research were actively discussed at the Workshop.

Finally, two important human diseases associated to protein aggregation due to misfolding were addressed at the Workshop: amyloid related diseases (including Alzheimer's disease) and transmissible encephalopathies caused by a proteinaceous infections agent or prion. Not only invited papers but also the communications presented as posters in this Workshop were important contributions to grasp the current state and the future work to do on this fascinating biological problem. While many of the questions on protein folding are still to be solved, the Workshop did certainly succeed in enriching our view of the problem and setting the scenario for future developments on the field.

A. R. Fersht, M. Rico and L. Serrano

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1998 Fellowships

1998 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 a 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 1998, 93 of these fellowships were awarded to participants in 14 different meetings. Among these, 22 fellowships were granted to scientists working in Spain, and 71 to scientists working abroad.

XVII 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 1998, the XVII lectures series took place, with the general theme of **SIGNALLING THROUGH TYROSINE PHOSPHORYLATION**. The speakers and topics were as follows:

2 March

EDMOND H. FISCHER
Department of Biochemistry
University of Washington
Washington, Seattle (USA)
1992 Nobel Prize in Medicine

Cell regulation by protein phosphorylation.

Introduced by: **Carmelo Bernabeu**
Centro de Investigaciones Biológicas
Madrid

9 March

TONY HUNTER
The Salk Institute
American Cancer Society Research
San Diego, CA. (USA)

Structure and function of tyrosine kinases and phosphatases.

Introduced by: **César de Haro**
Centro de Biología Molecular "Severo Ochoa"
Universidad Autónoma de Madrid

16 March

JOSEPH SCHLESSINGER
Department of Pharmacology
New York University Medical Center
New York NY. (USA)

Mechanism of action of growth factor receptors.

Introduced by: **Flora de Pablo**
Centro de Investigaciones Biológicas
Madrid

23 March

JAMES E. DARNELL
Laboratory of Molecular Cell Biology
The Rockefeller University
New York, NY. (USA)

Signalling genes from the cell surface.

Introduced by: **Rafael Fernández Muñoz**
Hospital Ramón y Cajal
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 1998, these were as follows:

During the workshop on **Ion Channels** (30 November-2 December):

- **NIGEL UNWIN**
  Laboratory of Molecular Biology
  Medical Research Council
  Cambridge (UK)

  How do ion channels work? - recent insights from electron images

- **RODERICK MACKINNON**
  Howard Hughes Medical Institute
  Rockefeller University
  New York (USA)

  Potassium channels

Introduced by: **Juan Lerma**
Instituto Cajal, C.S.I.C.
Madrid (Spain)

During the workshop on **Protein Folding** (14-16 December):

- **ALAN R. FERSHT**
  Cambridge University Chemical Laboratory
  Cambridge (UK)

  Protein folding and cancer

- **LUIS SERRANO**
  European Molecular Biology Laboratory
  Heidelberg (Germany)

  Advances in protein design

Introduced by: **Manuel Rico**
Instituto de Estructrura de la Materia, C.S.I.C.
Madrid (Spain)

Reviews in Scientific Journals

REVIEWS IN SCIENTIFIC JOURNALS

During 1998, the meetings organized by the Centre have been reviewed in the following articles and books:

Akam, M. (1998). The Yin and Yang of Evo/Devo. **Cell 92:** 153-155. (On the workshop on *Development and Evolution*, held in November 1997).

Khan, S. A. and Chattoraj, D. K. (1998). Initiation of DNA Replication in Phages and Plasmids – A Workshop Summary. **Plasmid 40:** 1-11. (On the workshop on *Initiation of Replication in Prokaryotic Extrachromosomal Elements*, held in February 1998)

Linden, D. E. J. (1998). Visual perception: myths and mechanisms. **Trends in Neurosciences 21 (6):** 225-226. (On the workshop on *Mechanisms Involved in Visual Perception*, held in February 1998).

Bray, S. (1998). A Notch Affair. **Cell 93:** 499-503. (On the workshop on *Notch/Lin-12 Signalling*, held in March 1998).

Lamas, S., Pérez-Sala, D. and Moncada, S. (1998). Nitric oxide: from discovery to the clinic. **Trends in Pharmacological Sciences 19:** 436-438. (On the workshop of the same title, held in June 1998).

Oxygen Regulation of Ion Channels and Gene Expression (1998). Eds. J. López-Barneo and E. K. Weir. Futura Publishing Company, Inc. Armonk, N.Y. (Based on the workshop of the same title, held in November 1996).

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 on *Transcription Factors in Lymphocyte Development and Function*, held in October 1998).

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.** Inst. 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. 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**	**S.C. West.** Imperial Cancer Research Fund. Herts. **S. Kowalczykowski.** University of California. Davis. **J.C. Alonso.** Centro Nacional de Biotecnología. Madrid. **J. Casadesús.** Facultad de Biología. Universidad de Sevilla.
26-28 April	**Neutrophil Development and Function**	**L.A. Boxer.** University of Michigan. Ann Arbor. **F. Mollinedo.** Facultad de Medicina. Universidad de Valladolid.
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**	**C.W. Greider.** Johns Hopkins University. Baltimore. **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**	**J.H.J. Hoeijmakers.** Erasmus University. Rotterdam. **A. Aguilera.** Facultad de Biología. Universidad de Sevilla.
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. **M. Navarro.** Fac. de Psicología. Universidad Complutense de Madrid. **F. Rodríguez de Fonseca.** Facultad de Psicología. Universidad Complutense de Madrid.

Index of Personal Names

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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