Instituto Juan March
de Estudios e Investigaciones

75

CENTRO DE REUNIONES
INTERNACIONALES SOBRE BIOLOGÍA

1997
Annual Report

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

Every issue of a scientific journal, every scientific conference, and every informal meeting between scientists is devoted to testing current orthodoxy in order to see whether it can be improved. Science is a stumbling process toward change.

John Polanyi (1997). Science 277, 881.

INSTITUTO JUAN MARCH DE ESTUDIOS E INVESTIGACIONES

CENTRE FOR INTERNATIONAL MEETINGS ON BIOLOGY

1997 ANNUAL REPORT

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FOREWORD

This publication covers the activities of the Centre for International Meetings on Biology during the year 1997. 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 1997 was the organization of eleven workshops and a practical course, dealing with very different biological topics. An additional symposium took also place, in coincidence with the 100th meeting organized by the Centre. 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, 243 speakers were invited to the 1997 meetings, and 559 participants were chosen from among the 709 applications received.

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 1997, 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 1997 in scientific journals, regarding meetings organized by the Centre.

The schedule of meetings to take place in 1998 is also offered in this book.

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
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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**.

1997 Meetings Schedule

CENTRE FOR INTERNATIONAL MEETINGS ON BIOLOGY

1997 MEETINGS SCHEDULE

Date	Meeting Subject	Organizers
10-12 February	**TGF-ß Signalling in Development and Cell Cycle Control**	**J. Massagué.** Howard Hughes Medical Institute. New York. **C. Bernabeu.** Centro de Investigaciones Biológicas. Madrid.
10-12 March	**Novel Biocatalysts**	**S. J. Benkovic.** The Pennsylvania State University. University Park. **A. Ballesteros.** Instituto de Catálisis y Petroleoquímica. Madrid.
21-23 April	**Signal Transduction in Neuronal Development and Recognition**	**M. Barbacid.** Bristol-Myers Squibb Pharmaceutical Research Institute.Princeton. **D. Pulido.** Centro de Biología Molecular "Severo Ochoa". Madrid.
12-13 May	**100th Meeting: Biology at the Edge of the Next Century**	**Centre for International Meetings on Biology. Madrid.**
26-28 May	**Membrane Fusion**	**V. Malhotra.** University of California, San Diego. La Jolla. **A. Velasco.** Facultad de Biología. Universidad de Sevilla.
9-11 June	**DNA Repair and Genome Instability**	**T. Lindahl.** Imperial Cancer Research Fund. Herts. **C. Pueyo.** Facultad de Ciencias. Universidad de Córdoba.
7-19 July	**Biochemistry and Molecular Biology of Non-conventional Yeasts**	**J. M. Cregg.** Oregon Graduate Institute of Science and Technology. Portland. **C. Gancedo.** Instituto de Investigaciones Biomédicas. Madrid. **J. M. Siverio.** Facultad de Biología. Universidad de La Laguna.
22-24 September	**Principles of Neural Integration**	**C. Gilbert.** The Rockefeller University. New York. **G. Gasic.** Neuron Editorial Offices. Cell Press. Cambridge. **C. Acuña.** Facultad de Medicina. Universidad de Santiago de Compostela.
6-8 October	**Programmed Gene Rearrangement: Site-Specific Recombination**	**N. D. F. Grindley.** Yale University. New Haven. **J. C. Alonso.** Centro Nacional de Biotecnología. Madrid.
20-22 October	**Plant Morphogenesis**	**M. Van Montagu.** University of Gent. **J. L. Micol.** Facultad de Ciencias. Universidad de Alicante.
3-5 November	**Development and Evolution**	**W. Gehring.** Biozentrum. University of Basel. **G. Morata.** Centro de Biología Molecular "Severo Ochoa". Madrid.
1-3 December	**Plant Viroids and Viroid-Like Satellite RNAs from Plants, Animals and Fungi**	**H. L. Sänger.** Max-Planck-Institut für Biochemie. Martinsried. **R. Flores.** Instituto de Biología Molecular y Celular de Plantas. Valencia.

1997 Workshops

TGF-β Signalling in Development and Cell Cycle Control

Organized by
J. Massagué and C. Bernabéu.

(10-12 February)

The proliferation and differentiation of cells in higher organisms is controlled by extracellular polypeptides known as "growth factors" or "cytokines". These factors are produced by many cell types and act on neighboring cells, forming an intercellular signaling network. Growth factors exert their effects by contacting receptor proteins on the membrane of target cells. Based on the enzymatic activity on their cytoplasmic half, these receptors can be grouped in three major classes: the G protein-coupled receptors, the tyrosine kinase-coupled receptors and the receptor serine/threonine kinases. Much work over the past two decades has been directed towards identifying these receptors and understanding the biochemical mechanisms that carry and translate their signals into specific effects on cell division, differentiation and death processes.

TGF-β and related factors constitute one of the most diverse and fascinating families of growth factors. Factors of the TGF-β family are present in organisms ranging from the fruitfly to man, and are involved in controlling crucial steps during embryogenesis as well as maintaining and repairing adult tissues and functions. Three years ago, the receptor mechanism employed by TGF-β was elucidated with the finding that this factor binds to a receptor serine/threonine kinase known as the "type II" receptor. Upon binding, the type II receptor recruits, phosphorylates and activates a related kinase, known as the "type I" receptor, which then propagates the signal by phosphorylating in turn other proteins. Other members of the TGF-β family such as the activins and the bone morphogenetic proteins (BMPs) seem to employ a similar receptor mechanism. This process of receptor activation is highly regulated. In fact, in addition to these receptor kinases, TGF-β interacts with another class of membrane receptors known as the "type III" receptors. This class includes two important molecules, betaglycan and endoglin, which are specialized in controlling the access of TGF-β to the signaling receptors.

During the past year, a series of milestone findings have allowed for the first time to piece together a pathway linking these receptors to their target genes in the nucleus. The first breakthrough came through studies on the Dpp pathway in the fruitfly *Drosophila*. Dpp is the fly homologue of the vertebrate proteins BMP-2 and BMP-4, and plays key roles during development of the embryo and the larva. Recently, genetic screens for mutations that would exacerbate the phenotype of defective Dpp receptors led to the identification of a gene called Mad. A family of Mad homologues, known as Smad proteins, were quickly identified in human, mouse, frog and nematode. More importantly, the Smads were rapidly shown to act downstream of the receptors for TGF-β, activin and BMP. Furthermore, biochemical analysis of the Smad proteins has demonstrated that they are the direct substrates of the type I receptors. Upon phosphorylation by the receptor, the Smad proteins move from the cytoplasm into the

nucleus. Once in the nucleus, Smads are thought to associate with subunits with specific DNA binding activity generating complexes that directly control gene expression. Smads associate with themselves in trimers of diverse composition, generating a combinatorial systems that may underlay the functional complexity of the TGF-β family. This year has therefore witnessed the dawn of the TGF-β/Smad pathway.

Although the TGF-β family has many effects on virtually every cell type, certain cellular responses to these factors have attracted special attention because of their biological significance. Examples include the ability of TGF-β to inhibit cell proliferation, to stimulate cell adhesion and migration, and to suppress immune cell function, as well as the ability of activin and BMP to induce the formation of mesoderm in the frog, and the ability of Dpp to control wing and eye formation in *Drosophila.* Some of the genes mediating these responses have been identified. For example, TGF-β activates the expression of p15, a protein that inhibits cyclin-dependent kinases (CDKs). CDKs are essential for cell commitment to DNA replication and mitosis, and constitute a major nexus of positive and negative growth stimuli. CDK inhibitors such as p15, p16, p21 and p27 represent one of the principal controls over the activity of these kinases. Work is in progress to determine whether p15 and other gene responses to TGF-β and related factors are directly mediated by the Smads.

Progress in understanding the mechanisms of TGF-β signaling is beginning to shed light into the molecular basis of several important disease conditions. Disruption of the TGF-β growth inhibitory mechanism is often observed in human cancer. Almost all cases of a certain form of human colon cancer have lost the TGF-β type II receptor whereas a majority of human pancreatic carcinomas have lost Smad4/DPC4, a Smad family member required for signaling by all TGF-β factors. When the growth inhibitory response to TGF-β is lost, cells may be left with the ability to migrate and invade tissue in response to this factor. Indeed, studies on TGF-β transgenic animals have shown that skin and mammary carcinoma cells become much more invasive when they are stimulated by TGF-β. A completely different type of pathology originates when deleterious mutations appear in the gene encoding endoglin, a component of the membrane TGF-β receptor system. Endoglin in chromosome 9q34, is the target gene for Hereditary Hemorrhagic Telangiectasia type 1 (HHT1), also kown as Rendue-Osler-Weber syndrome. HHT is an autosomal dominant vascular disorder associated with frequent nose bleeds, telangiectases, and lung and brain arteriovenous malformations. These abnormalities are probably due to a defect in the TGF-β responses of the endothelial cells.

In experiments with animal models, the generation of TGF-β knockout mice have unveiled non-overlapping phenotypes among the β1, β2, or β3 isoform null animals. These knockout mice indicate that during embryogenesis TGF-β1 functions in preimplantation development and implantation, and in the adult it prevents autoimmunity. On the other hand, TGF-β2 plays an important role in epithelial-mesenchymal interactions in the development of the cranial, axial and appendicular skeleton, eyes and ears, heart, and urogenital tract. TGF-β3 plays an essential role in secondary palate fusion. An important finding is that the viability of the TGF-β1 knock out mice highly depends on the genetic background, suggesting the existence of genetic modifiers and opening new avenues in the characterization of the corresponding genes.

In summary, it appears that in spite of the high complexilty of the TGF-β system, the TGF-β field has undergone important advances which are helping to integrate and understand its genetic, molecular, cellular and developmental implications as a whole.

Joan Massagué and Carmelo Bernabéu

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Novel Biocatalysts

Organized by
S.J. Benkovic and A. Ballesteros.

(10-12 March)

The finding of new catalysts and of molecules that rival natural enzymes in their substrate specificity and catalytic turnover is of a major importance in the production of compounds for use in pharmaceuticals, in the development of novel biosensors, and in the actual *in vivo* use of such molecules to treat human disease. Besides these practical considerations, the insights furnished by such efforts into the functioning and organization of catalytic biomolecules in cellular development and reproduction contribute to answering key contemporary questions in biology.

The present approaches to the creation of novel catalysts fall into two general categories: the *de novo* design and synthesis of catalysts from organic molecules such as macrocycles, polymers, cyclodextrins and peptides; and the modification of existing catalysts such as enzymes or ribozymes by genetic or chemical methods. Abzymes can be considered a hybrid of the two that uses design and synthesis to create a transition state analogue which in turn is used to tap the immunological response for putative proteinaceous catalysts. Advances in these areas include the construction of ribozymes capable of cleaving a viral DNA target; the induction of catalytic antibodies that promote stereospecific ester and peptide synthesis or disfavored chemical reactions; the formulation of enzymes to function in organic solvents; and the modification of enzymic activity to broaden substrate specificity to mention several. These advances have been associated with equally valuable "spin-off " technology: for example the cloning and expression of antibody fragments in bacteria, improvements in solid state peptide synthesis, and computer modeling of structures.

These and other recent advances set the stage for examining key issues such as: minimal catalyst size, the importance of long range molecular forces for substrate specificity and optimal turnover, the development of computer methods with predictive capabilities, the definition of novel medical targets within the scope of available catalysts and the applications of such catalysts to organic synthesis.

The present Workshop provided an opportunity for interdisciplinary researchers to discuss many of these issues:

- Sessions on enzymes provided an opportunity for examining the catalytic efficiency of enzymes relative to the spontaneous reaction for a given process. The range of catalytic efficiencies of enzymes has proven to be enormous, from a factor of 10^6 to one as high as 10^{24}. Interestingly the enzyme catalyzed rates for all of these processes fall in the same time domain as would be required by the network of reactions in a living organism. How these marvelous machines evolved from ancestral families appears to be within our grasp, since powerful algorithms allow one to reconstruct the primordial genes and through modern recombinant techniques to express these proteins and to study their catalytic function. There are still a large number of organisms that have not been examined for their ability to catalyze specific reactions,

but with the growing genomic databases the range of reactions catalyzed by enzymes will certainly expand. Consequently, powerful screening techniques need to be developed for not only exploring the nature of enzymes in various organisms but also the properties of recombinant enzymes that are members of large combinatorial libraries. Moreover, enzymic catalysis is no longer restricted to aqueous media, there is considerable evidence that enzymes function in nonaqueous media where their catalytic as well as stereospecificity can be manipulated.

- The engineering of enzymes either by recombinant methods or chemical means holds considerable promise for extending the stereospecificity and regioselectivity of many enzymes. Recognizing that enzymes can often be divided up into discreet domains, the possibility of swapping these domains to create novel catalysts with changed cofactor specificity or reaction characteristics seems within reach. Many of these changes will be non-rational and cannot be predicted from existing structural databases. They will require phage display or other forms of combinatorial libraries. The resulting materials may be composites between naturally occurring amino acids and other organic reagents that can be introduced either by synthetic or recombinant methods. In fact, at one extreme molecular imprints can be created from polymeric materials that allow the formation of artificial binders and biocatalysts with altered substrate specificity.

- A fundamental tenet of enzymic catalysis is the principle of transition state stabilization that underlies many of the explanations for an enzymes superior catalytic efficiency. Reexamination of this issue by both model systems as well as computational methods suggest that some of these beliefs may not be that well founded. For example, computational methods suggest that the enthalpic rather than the entropic term might be of paramount significance in the formation of the enzyme's substrate complex and its increased reactivity. In fact the ground state, enzyme substrate complex may be in a more reactive conformation than originally thought providing an impetus for the examination of such species by a variety of spectroscopic methods. The complexity of enzymic catalysis has always been subjected to dissection by a variety of model studies and those involving supermolecular complexes which follow enzyme-like kinetics in processing their substrates, may provide valuable insights as to the importance of rigidity vs. dynamics in the catalytic process.

- Ribozymes and abzymes have now appeared on the scene as another form of biological catalyst, the former naturally occurring and the latter manmade. A key question here is to whether these catalysts can be crafted to improved catalytic

efficiencies, or perhaps more importantly what they tell us about enzyme function. Ribozymes and abzymes hold great promise as *in vivo* therapeutic agents.

Because catalysis cuts across so many disciplines, this meeting was particularly important because it brought together a number of practitioners that view this subject from different aspects. Some were grounded in the practicality of finding enzymes or catalysts for specific application, others were more interested in the fundamentals of how enzymes function, how they were designed, how they evolved, and still others were making a strong effort to build catalysts through synthetic or combinatorial methodologies. All agreed that the experience of finding a common language for communication as well as the opportunity to discuss issues in depth made this meeting most valuable and memorable.

Stephen J. Benkovic
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Signal Transduction in Neuronal Development and Recognition

Organized by
M. Barbacid and D. Pulido

(21-23 April)

The development of the nervous system requires the proliferation of neuronal precursors, their migration to their respective locations, their differentiation into mature cells, and their survival since most nervous cells cannot be replaced. Moreover, the proper functioning of the nervous systems requires that neurons extend their axons according to a precise pattern so they reach their corresponding targets. Over the past several years, the molecular components responsible for neuronal survival and differentiation, as well as for axonal guidance are being defined with the discovery of new soluble or cell-attached factors, their cognate receptors, and their corresponding signal transduction pathways.

Neurons, the basic cellular components of the nervous system, control our autonomic, sensory and cognitive activities. Remarkably, neurons are only generated during early development. Since neuron are post mitotic cells, that is they cannot divide, our organism has to provide the means to maintain these cells alive and functional during our entire life span. Therefore, understanding the molecular mechanisms that control the generation of neurons from neuronal precursors during development as well as their long-term adulthood, is one of the major challenges in biomedical research today. Invariably, as our organism senesce, a certain population of neurons die and cannot be replaced. However under some pathological conditions such as Amyotrophic Lateral Sclerosis, Parkinson's and Alzheimer's disease, the process of neuronal degeneration becomes considerably accelerated resulting in significant loss of motor neurons and/or cognitive functions. Only when we can understand the cascade of events that led to premature neuronal cell death, we will be in a position to rationally prevent, or at least palliate, the pathological consequences of these neurodegenerative diseases.

During the last few years, we have witnessed several important developments in the field of signaling during neural development. For instance, several new neurotrophic factors have been discovered. Moreover, their receptors have been identified, thus making it possible to decipher the signal transduction pathways that mediate their neurotrophic properties. Mice defective in these neurotrophic molecules have also been generated by gene targeting approaches. These animals have provide the necessary tools to study the role of these molecules in neuronal differentiation and survival in vivo. More recently, three families of proteins, the netrins, the Eph family of tyrosine protein kinase receptors and their cognate ligands (known as ephrins) have been implicated in axonal guidance and possibly in the establishment of topographic maps. The expression of ephrins and Eph receptors in complementary gradients during the development of the nervous systems suggests that these molecules may act as cues for axonal guidance. The

generation of gene-targeted mice defective in some of these molecules should provide relevant information to determine the physiological role of these molecules in the development of the mammalian nervous system

The Juan March Workshop on "Signal Transduction in Neuronal Development and Recognition" held on April 21-23, 1997 provided a major opportunity to bring together an international group of prominent investigators working in these areas to survey and discuss the state of the art of signal transduction during neuronal development. Several topics were addressed at this meeting including neurotrophic factors and signal transduction, neuronal differentiation and survival and neural patterning during development. The second half of the meeting focused on a series of recently identified molecules involved in axonal guidance and recognition. Several talks were dedicated to the Eph receptors and their cognate ligands and their possible role as positional labels. The generation of mice lacking these molecules also revealed unexpected roles for these molecules during early development. The characterization of gene-targeted mice lacking netrins and their receptors illustrated the positive role that these novel class of molecules play in axonal guidance. Finally, the role of three other classes of molecules in axonal guidance processes, the semaphorins, certain tyrosine phosphatases and the Ras-like protein, Rac1, was illustrated by using elegant genetic experiments.

In summary, this Workshop provided the ideal forum to present the state of the art of two of the most exciting areas in neurobiology, the signaling mechanisms that control the growth and differentiation of neuronal cells and the identification of the molecular elements that guide axons to their physiological targets.

M. Barbacid and D. Pulido

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Membrane Fusion

Organized by
V. Malhotra and A. Velasco

(26-28 May)

Membrane fusion is essential for the formation of myoblast, cell division, organelle assembly, protein transport in vesicle fission and fusion. An understanding of this process is therefore of fundamental importance. At the recent meeting on "membrane fusion" it became clear that significant progress has been made in our understanding of the process but a lot is still unknown.

A variety of approaches have led to the identification of important components of the fusion machinery. The major known components such as NSF, SNAPs, SNAREs, Rabs, proteins involved in phosphoinositide metabolism, and other accessory proteins were discussed at the meeting. Some of the more recent surprises regarding the role of these components are: NSF can act prior to docking of the fusing membrane, v - and t-SNAREs align in a parallel fashion on the opposing fusing membranes, not all v-SNAREs are essential for survival, the overall structures of NSF, P97 and hsp 104 revealed by electron microscopy are very similar and some fusion events do not require NSF and SNAPs. A suggestion was made to consider the paired SNAREs equivalent to the haemagglutinin (HA) molecules that are anchored in both the viral and the cellular membrane. In both cases, a ring of these membrane-anchored molecules appears to form a fusion pore. It was concluded that the SNAREs play a central role in membrane fusion, but their role in docking/targeting is less clear. This is a general problem because assays to distinguish clearly between the docking and the fusion steps are not presently available.

Lipids and lipid metabolites which are essential components of the fusion machinery are also being revealed, although like their partners (i.e., proteins) the exact role is far from clear. It is also not obvious whether all the protein components involved in the terminal stages of the fusion process have been identified or if there are many unknowns after the t-SNAREs. One should also remember that no SNAREs, or their close cousins, have been found on mitochondria and peroxisomes, which also rely on fusion for growth and division. The events regulating vesicle fission (during the budding process) are also likely to involve a different mechanism and therefore will continue to generate new twists in the ongoing quest.

The electrophysiologists are developing very clever assays to obtain a kinetic analysis of the terminal stages of the docking and fusion events. Mice defective in specific proteins should not only reveal their significance in the fusion event but also help determine the physiological role of these molecules in the development of synaptic junctions and the nervous system.

Surprisingly, there are a number of new members identified by genetic trickeries using the simple organism yeast for which an exact role in the terminal stages of the secretory pathway is presently not known. The requirement for G-proteins and GTP-hydrolysis is clear, but the exact functions which are being regulated is still rather controversial.

In other words, as concluded by some "that we are more or less there" may be a bit premature. It is however clear that the enthusiasm to address this problem at the molecular level is only going to escalate, and therefore the next meeting in a decade or so on this topic will have (hopefully) all the details.

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DNA Repair and Genome Instability

Organized by
T. Lindahl and C. Pueyo.

(9-11 June)

A multitude of endogenous and environmental mutagens cause structural damage to cellular DNA, and DNA replication errors also occur as infrequent chance events. Three different DNA excision-repair pathways (base excision-repair, nucleotide excision-repair, and mismatch repair) provide a first line of defense against such alterations, and these pathways have been largely conserved from microorganisms to man. In recent years, cloning of human cDNAs encoding key repair factors, and their functional expression leading to reconstitution of the repair pathways, have greatly improved our understanding of these cellular defense systems.

The association between defective DNA repair and certain forms of human cancer has stimulated research in this area. Defective nucleotide excision-repair in man is detected clinically as xeroderma pigmentosum, a syndrome associated with greatly elevated levels of skin cancer after sun exposure. Ultraviolet light from the sun is, by far, the most important environmental mutagen (except for chain smokers) and the nucleotide excision-repair system evolved early to counteract ultraviolet-induced DNA damage. The recent reconstitution of the complex human pathway with purified proteins has defined the major steps in the process, but less well understood accessory protein factors may be required for optimal repair. Base excision-repair is primarily employed to remove DNA damage caused by endogenous events, and the human pathway(s) have also been reconstituted with purified proteins.

The recently established correlation between defective mismatch repair and a common form of colon cancer in man resulted in broadened interest in this form of DNA repair, and related problems of gene instability. It is an intriguing possibility that an early cellular event during tumorigenesis might be the generation of a mutator phenotype. An emerging important factor here is the epigenetic methylation of DNA. Tumor cells often have complex altered methylation patterns, and the introduction of new technology such as the bisulphite method for sequencing methylated DNA now allows comprehensive studies of this form of DNA perturbation. It is already known that 5-methylcytosine residues in DNA are hot spots of mutation, as strikingly observed in mutated p53 sequences, because the hydrolytic deamination product of 5-methylcytosine is thymine - the resulting guanine-thymine base-pairs are corrected only with difficulty by a DNA glycosylase present at very low levels, because the mismatch repair system requires a strand discrimination signal only available in newly replicated DNA.

Transgenic mice are becoming increasingly important for studies of genomic instability, and knockout mice defective in one or the other of most well characterized DNA repair functions are now available. Excellent animal models of different complementation groups of xeroderma pigmentosum, Cockayne's syndrome, and trichothiodystrophy have been constructed. Crosses between different strains to produce double knockouts are carried out in several laboratories, and are further elucidating the

various steps and controls of repair events. These projects include the large protein kinases which have been shown recently to be involved in control of growth arrest, ATM being most intensely studied. A return to biochemical experimentation is now required to address key questions such as the identification of the relevant substrates for the ATM and DNA-PK_{cs} protein kinases, and the mechanism(s) by which DNA damage causes an increase in cellular levels of p53.

Rejoining of DNA double-strand breaks occurs largely by non-homologous recombination in mammalian cells, and the factors involved are being characterized. It is important to minimize translocation events, but on the other hand broken DNA requires rejoining. The mechanisms that control and fine-tune such processes will be scrutinized over the next years. Such investigations should also help to clarify special problems such as the preservation of telomere integrity, which might require recombinational repair and telomere binding proteins in addition to telomerase. Unique, highly important biological processes such as processing of antibody genes also may depend on special repair and recombination events. In this regard, recent characterization of V(D)J joining has provided detailed understanding of this process, partly thanks to the availability of a cell line that carries out this form of DNA joining. The fascinating events of hypermutation and class switching still await similar detailed explanation, but key facts about the mechanisms involved are gradually being unravelled.

The Juan March workshop on "DNA repair and genome instability" held on June 9-11, 1997, provided a timely and stimulating review of this major field of cancer research.

Tomas Lindahl and Carmen Pueyo

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Principles of Neural Integration

Organized by
C. Gilbert, G. Gasic and C. Acuña.

(22-24 September)

Studies on the cellular basis of perception and behavior have revealed fundamental new ideas concerning how information is encoded by the nervous system. It is now possible to establish links between the activity of individual neurons and of neuronal ensembles to complex behaviors. There is still considerable debate, however, concerning the conceptual framework by which one should establish such linkage, and the symposium on Principles of Neural Integration was designed to frame the debate on several key issues.

The information carried by neurons can be expressed as a "rate code", in which all that counts is the number of action potentials per unit time, or as a temporal code, in which stimulus information is represented by the precise pattern of impulses over time. The timing of impulses for one neuron may reflect synchronization within an ensemble of cells participating in a larger network. The relative contributions of rate and temporal codes can be measured by using information theory, where the amount of information carried different components of cells' responses to a range of stimuli can be quantified. One argument for the need for temporal codes is to deal with the problem of how to link the components common to particular objects and to segment components belonging to different objects. It is argued, alternatively, that the linkage operation is reflected in changes in the firing rates of cells, whose response depends not only on the characteristics of local features but also upon the global characteristics of contours and surfaces within which those features are embedded. The issue of how one can identify multiple objects within a scene, may be dealt with by attentional mechanisms, where the scene can be dealt with one object at a time.

Another important issue is how sensory information is linked to motor output, and how extrapersonal space is represented. Two model systems that have provided important information on these issues are the superior colliculus and the parietal cortex. Attention has played an important role in this analysis, and has been considered along with intention as playing an important modulatory role.

A third issue explored in the symposium is the role of dynamic changes in cortical circuits and receptive field properties. Parallel studies in human psychophysics and cortical receptive field properties have demonstrated the role of context in shaping the perception of stimulus attributes, the role of experience or perceptual learning, and the role of visuospatial attention. These influences are seen throughout the cortical visual pathway, from the primary visual cortex to parietal cortex and to visual areas in the temporal lobe. The circuitry underlying these different forms of plasticity include lateral

interactions within individual areas and feedback connections from higher to lower order areas.

The highest order aspects of memory and perception have become much more accessible to study, and there are a number of elements in the higher order properties of cells that are characteristic of cortical areas. Complex representations of object identity and of the local environment are represented in the temporal cortex and hippocampus. The interaction between high order areas allow for the storage of this information, and interactions between high and lower order sensory areas give the earlier stages much more complex properties that traditionally believed. Exploring the interaction between memory systems in the limbic areas and the higher order sensory areas in the temporal lobe is one of the greatest challenges in the field of neural systems. The joining together of behavioral analysis, responses of individual neurons and of neuronal ensembles, and mathematical models, is providing a groundwork for understanding the brain mechanisms of even the most complex percepts and behaviors.

C.D. Gilbert and G. Gasic

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Programmed Gene Rearrangement: Site-Specific Recombination

Organized by
N.D. F. Grindley and J.C. Alonso

(6-8 October)

Site-specific recombination, sometimes qualified by the term 'conservative site specific recombination', is a process that involves the reciprocal exchange of defined DNA segments by precise breakage and rejoining mechanisms with no loss or synthesis of DNA. A particular feature of such processes is that phosphodiester bond energy is conserved throughout the reaction. DNA breaks are made not by hydrolysis but rather by phosphoryl transfer to a side chain (a tyrosine or a serine) of the recombinase, resulting in covalent linkage of the enzyme to the terminal phosphate of the broken DNA. DNA is resealed, and the recombinase released, by reversal of the process - attack by the terminal hydroxyl of the DNA on the protein-DNA phosphodiester.

Biological roles of site-specific recombination (thus defined) include chromosomal integration and excision of bacteriophage genomes, monomerization of plasmid and bacterial chromosomes, switching of gene expression between two alternative modes, resolution of transposition intermediates and the fusion of gene cassettes into a functional gene. The vast majority of site-specific recombinases fall into two distinct groups: the Integrase family, named after the prototypical phage λ integrase, and the Resolvase family, named after the cointegrate resolving proteins encoded by the transposons, γδ and Tn*3*. Members of the integrase family include λ and many other phage integrases, the phage P1 Cre protein and the bacterial XerC and XerD proteins, the FLP protein encoded by the yeast 2μm circle, the integron-associated recombinases (responsible for the acquisition of antibiotic resistance cassettes) and the transposases of conjugative transposons. The resolvase family includes most transposon-encoded resolvases, DNA-invertases such as Hin and Gin, and a few phage integrases. These two families are unrelated in protein sequence or structure, and employ different recombinational mechanisms. In this Workshop, about half of the sessions were devoted to presentation and discussion of the latest results obtained with members of these two families (including the crystal structure of a synaptic complex).

Recombination using specific sites is, however, not the exclusive domain of the Integrase and Resolvase family of proteins. Nor are the processes used by these recombinases, such as the site-specific cleavage of DNA; the pairing of distant DNA segments to form synaptic complexes; and the formation of covalently linked protein-DNA intermediates. The other half of the Workshop was focussed on biological processes that exhibit one or more of the features found in site-specific recombination.

In mammalian cells, the phenomenon closest to the conservative definition of site-specific recombination is the rearrangement of the immunoglobulin and T-cell receptor genes that accompanies B-cell and T-cell development. Specific DNA sites are brought

together in synaptic complexes by the Rag1/Rag2 recombinase, cleaved (without protein-DNA linkage), rearranged and rejoined. Although signal joints are precise, the coding joints are not and typically show addition or deletion of a few nucleotides. The process of synapsis was specifically addressed, as was the involvement and role of additional nuclear proteins. Synapsis also turns out to be an unexpected feature of the 'restriction' endonuclease, SfiI.

Workshop participants were informed about progress towards understanding three rather unusual recombination events, very different from conservative site-specific recombination, but site-directed nevertheless. One of these is the programmed deletion of thousands of genomic segments that occurs during macronuclear development in the ciliate, *Tetrahymena thermophila.* A new *in vitro* system was described which gave results supporting a novel mechanism for this deletion. The other two involve the 'homing' of DNA encoding group I and group II introns to intron-less genes. Homing occurs by very different mechanisms; in one case, involving directed gene conversion by double strand break repair; in the other, involving the direct participation of the intron RNA as well as the intron-encoded reverse transcriptase and other functions.

Initiation of conjugative DNA transfer and site-specific recombination are topics rarely found on the same programme at a scientific meeting. However, since both processes conserve phosphodiester bond energy and ensure precise reversibility by the formation of a covalently linked protein-DNA intermediate, relaxases from several plasmids were discussed in detail.

The breadth and depth of the topics presented, the relatively small number of participants, and the intimate and congenial atmosphere of the Juan March Institute combined to produce a highly informative meeting with lively and stimulating discussions.

J.C. Alonso and N.D.F. Grindley

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Plant Morphogenesis

Organized by
M. Van Montagu and J.L. Micol.

(20-22 October)

The architecture of pluricellular organisms is the result of complex cell mechanisms which obey genetic controls operating and interacting in specific spatial and temporal programs. To dissect such morphogenetic processes in animals genetic approaches have proven extremely helpful, although this cannot yet be said for plant developmental biology, a field which has only recently gone from descriptive approaches to causal analyses emphasizing in genetic and molecular methods. As an example of this, a relatively well known textbook on Plant Development by Lyndon (1990) states in its first paragraph "... three-dimensional form is specified in some way by the genes, *since there are genes for leaf shape, for example*, ...". Most, if not all biologists, would accept such an assertion, which appears to be common sense. However, available published data do not match common sense in this case, since the question of how a leaf is made remains largely unanswered at the genetic level. Nevertheless, the analysis of plant development is rapidly approaching the level of that of animals. In the past ten years, wide screens for mutations followed by epistasis analysis and molecular studies have been carried out and regulation models have been succesfully constructed particularly for flower development, a topic covered twice, in 1991 and 1995, in activities sponsored by the Fundación Juan March. In addition, information is becoming available on other aspects of plant development, since several research teams have focused their efforts on the genetic and molecular analysis of embryo and root development, meristem structure and functions, leaf organogenesis and pattern formation, the morphogenesis of some speciallized cells and cell organelles, the role of signalling mechanisms in plant-pathogen interactions, and the elements and paths of intercellular communication.

The study of plant development is in our days especially exciting, and has yielded much to help in our understanding of the molecular mechanisms that regulate pattern formation, the specification of cell fate and cell differentiation. Molecular genetics and biochemical approaches are defining an emerging picture on morphogenetic pathways and their interplay in space (organogenesis) and time (phase change). It is becoming clear that complex signalling networks are involved in the control of plant development and that cell to cell communication has consequences in the differentiation of plant cells.

It is not difficult to predict that new paradigms will arise in the years ahead from advances made in the study of mechanisms that determine pattern formation and those that regulate cellular differentiation in plants. The panoramic view on the present of plant developmental biology provided by the workshop covered in this book unequivocally points to a bright future for the field. Soon it will not be possible, as it is now, to maintain that the study of animal development is more advanced than that of plants.

José Luis Micol and Marc Van Montagu

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Development and Evolution

Organized by
W. Gehring and G. Morata

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The study of evolution has been a principal goal of biologists ever since Darwin published "The Origin of Species". After more than a century, a large amount of data has been accumulated, mostly from the fossil record and comparative anatomy and embryology. It has provided a historical picture of life in the planet; how different animal and plant phyla have appeared, flourished and in many cases extinguished. For many years the prevailing theme in these studies was the richness and diversity of animals. The differences between classes of animals -- mosaic versus regulative eggs, radial versus spiral cleavages, protozoa versus multicellular animals, annelids, arthropod, mollusks, versus echinoderms, ascidians and vertebrates -- were emphasized as a source of speculations on how they had evolved.

The irruption of molecular biology brought a revolution into the field of evolution, firstly providing novel ways to classify the different animal groups (especially from sequence comparison of rRNAs see, for example, Adoutte and Philippe, 1993), and secondly from the discovery of the universality of the major developmental mechanisms. In fact, the search for common mechanisms has been a driving force of Molecular Biology ever since the discovery of the universality of DNA or of the genetic code.

Considering only the Animal Kingdom, there presently are over two millions species that show a overwhelming diversity of sizes, shapes and life cycles. It is hard to imagine that there may be some general unifying principles behind that seemingly intractable complexity. And yet we are finding that those principles exist. The formation of new species during evolution is in essence the generation of new forms and shapes of body parts, so it is intimately connected with modifications in the functioning of developmental processes that generate morphological variations. That is, the explanation of the divergence that occurred during evolution will require the understanding of developmental processes.

During the last decade we have witnessed very significant progress in the field of Developmental Biology, in the larger part due to the introduction of the new molecular hardware: There have been profound insights into problems such as the generation of the diversity along the anteroposterior or proximal distal body axes or the signalling mechanisms underlying pattern formation. It has to be said that the leading edge has been the fruitfly *Drosophila*, while other model organisms like the mouse or the nematode *C. elegans* followed track. Typically, the genes involved with a particular process have been identified in the fly and subsequently the homologue genes have been found in other organisms, usually the mouse. The next step concerns the mechanism, which once has

been worked out in the fly, it has been shown to operate also in the other species.

A paradigmatic case is the *Hox* complex. The *Hox* genes had been studied (under another name) in *Drosophila* for more that 60 years and genetic studies (see Lewis, 1978) have determined that: 1) they generate much of the body's morphological diversity, 2) they probably function by regulating the activity of other, subsidiary, genes, 3) they are clustered in the chromosome, 4) they function following a collinear rule, and 5) they probably derive from a common ancestor.

The advent of molecular biology, and in particular the discovery by the groups of Walter Gehring and Matt Scott of the homeobox, which encodes a DNA binding polypeptide, provided a molecular marker for *Hox* genes and suggested a molecular mechanism of *Hox* function based on transcriptional regulation. But above all, the homeobox provided a key to enter into the genome of other organisms, worms, mice, humans, in which the *Hox* genes would have been very difficult or impossible to detect by conventional genetic analysis. It did not take long to demonstrate that all the properties described in *Drosophila* for the *Hox* complex applied to the mouse and generally to other organisms. The implication is that the generation of the morphological diversity along the A/P body axis follows a rule common to all animals and was invented only once in evolution. The conservation of structure and function of the *Hox* complex in species belonging to such distant animal phyla like Arthropods and Chordates implied the *Hox* complex had appeared before these groups diversified in the lower Cambrium, around 540 million years ago. This is the time when the famous Cambric explosion occurred, in which all extant animal groups suddenly appeared. It is hard to resists the temptation to speculate that the sudden emergence of so much morphological diversity is connected with the developmental invention of the *Hox* complex. The conservation affects not only to *Hox* complex itself, but also to cofactors like the *extradenticle* gene, that performs a similar function for the *Hox* complexes of *Drosophila* and the mouse.

It is worth mentioning that there are some body regions that do not have *Hox* gene activity but are instead specified by other genes. The development of anterior head requires *empty spiracles (ems), orthodenticle (otd)* and *buttonhead(btd),* two of which (*ems* and *otd*) are homeobox genes known to be conserved in vertebrates where they are expressed in the brain. At the other end of the body, the homeobox gene *caudal* specifies terminal structures and, correspondingly, the vertebrate homologues are also expressed in the posterior body regions where they presumably play a similar instructive role.

A high degree of conservation is also observed in other genetic processes not connected with the anterior posterior polarity of the body. The best known case is *Pax6*

(*eyeless*), a paired class gene found to be responsible for eye development in arthropods, mollusks and vertebrates. Work mainly from Walter Gehring's laboratory indicates eyes appeared only once in evolution and involved a genetic operation of which the gene *eyeless* (or its repeat *twin of eyeless*) is the triggering event. The same operation is still being used after 540 million years in the whole of the Animal Kingdom.

Finally, new insights have been made in the mechanism of pattern formation, until recently one of the least known of developmental phenomena. The gene *hedgehog* plays a central role in the cell patterning of *Drosophila* by itself and by inducing the activity of the other signalling genes decapentaplegic and wingless. The vertebrate homologue *Sonic hedgehog* is implicated in a positional signalling mechanism with many similarities to that found in *Drosophila*.

As mentioned above molecular biologists have accustomed us to think in terms of common principles, but not even the molecular biologists have prepared us for the universality of developmental mechanisms we are finding. This atmosphere of surprise still permeates every paper on this subject.

G. Morata and W.J. Gehring

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Plant Viroids and Viroid-Like Satellite RNAs from Plants, Animals and Fungi

Organized by
H.L. Sänger and R. Flores

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Twenty-five years after their discovery, viroids are still the only class of autonomously replicating subviral pathogens whose molecular structure is well defined. The sequences of 27 viroid "species" and of more than altogether 100 sequence variants thereof have been established. They show that viroids are composed by a coat protein-free single-stranded circular RNA chain in the size range between 245-399 bases. In some cases various aberrant forms, generated by sequence deletions and duplications, have been also described. The discovery of viroids has led to the modification of the paradigm established around the turn between the XIX and XX centuries considering viruses as the smallest known biological entities. In fact, viroids are currently the lowest step of the biological scale: they are molecular parasites at the frontier of life.

Viroids were discovered as a consequence of studies aimed at characterizing the agents of some plant diseases initially thought to be induced by viruses. Later on, they have been identified as the etiologic agents of a series of maladies affecting crops of economic importance: potato, tomato, citrus, hop, coconut, grapevine, several subtropical and temperate fruit trees as avocado, peach, apple, pear and plum, and ornamental plants as chrysanthemum and coleus.

Differences between viruses and viroids are not restricted to size but include also other structural and functional aspects. Viroids are circular RNAs with a high degree of secondary structure as a result of about 70% intramolecular self-complementarity. They adopt in most, but not in all cases, *in vitro* rod-like or quasi-rod-like conformations stabilized by elements of secondary and tertiary structure. From a more functional perspective all the available data support the contention that, in contrast to viruses, viroids do not code for any peptide or protein. Therefore, viroids must be replicated by a pre-existing host RNA polimerase(s), and they must elicit their pathogenic effects by direct interaction of their RNA with one or more cellular targets. Viroids can be regarded as parasites of the transcription machinery, whereas viruses are essentially parasites of the translation machinery.

Viroid-like satellite RNAs from plants share some structural properties with viroids: they have a similar size and they exist *in vivo* as circular and linear molecules. However, viroid-like satellite RNAs are not endowed with autonomous replication, and they are functionally dependent on helper viruses by whose coat protein they are encapsidated. Outside the plant kingdom there is so far only one member of this group: the human hepatitis delta agent, a satellite of hepatitis B which is responsible for a fulminant form of hepatitis. The RNA of hepatitis delta virus has also a circular structure and folds into a rod-like conformation. Viroid and viroid-like satellite RNAs also share a common strategy of replication. They follow a rolling circle mechanism with either a symmetric or asymmetric variant, and three main steps: RNA transcription, processing and ligation

catalyzed by enzymes with activity of RNA polymerase, RNase and RNA ligase, respectively. One remarkable aspect in this regard is that in some viroid and viroid-like RNAs the RNase activity is, instead of a enzyme, a ribozyme (see below).

More recently three viroid-like RNAs from animal, plant and fungal origin, respectively, have been discovered with a very peculiar property: they have a DNA counterpart. These observations clearly suggest the involvement of a reverse transcriptase activity in the generation of the corresponding DNA forms and, in fact, two of the aforementioned viroid-like RNAs have been found associated with two systems, a plasmid and a virus, encoding reverse transcriptases.

From an evolutionary perspective, viroid and viroid-like RNAs are also very intriguing systems. Their small size, circular structure and, especially, the frequent presence in their strands of ribozyme activities are suggestive indications that they could be molecular fossils of the RNA world which presumably existed on the Earth before the advent of cellular life.

One last point that deserves particular attention, because it has implications far beyond the limits of the specific research on viroid and viroid-like RNAs, is that these small RNAs have been the sources for most of the known synthetic ribozymes. The hammerhead- and hairpin- (or paperclip-) ribozymes have been found in three viroids and in all viroid-like satellite RNAs from plants, in which they catalyze in *cis* the processing of the oligomeric intermediates of the rolling-circle mechanism of replication. Due to their structural simplicity, these two ribozymes are being intensively manipulated to act in *trans* against target RNAs, like those of retroviruses, in what it is one of the most innovative and promising approaches in Biotechnology. Very recently, the first crystal structure of a ribozyme has been elucidated. The analysis of its hammerhead structure has provided insights into the mechanism by which the ribozyme may destabilize a substrate strand in order to facilitate the twisting that ultimately allows cleavage of the scissile bond. Other ribozymes derived from viroid-like RNAs of animal and fungal origin, those from hepatitis delta virus RNA and from the *Neurospora* VS RNA respectively, are also the subject of intensive research.

This Workshop brought together scientist actively engaged in working on viroid and viroid-like RNAs from plants, animals and fungi using molecular approaches.
The Workshop provided a unique opportunity for the participants to exchange and share information, to review and discuss new approaches, and to propose directions for future research.

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AIDS Vaccine

Organized by
D. Baltimore and M. Girard

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Acquired Immunodeficiency Syndrome (AIDS), has become one of the most important infectious diseases in the world. In fact, there are about 30 million people in the world today infected with Human Immunodeficiency Virus (HIV).

Even with the new antiretroviral drug therapies, it is still very much a problem. The drugs are very expensive and very hard to take; moreover, most of these therapies have toxic effects. For these reasons, they are not an optimal solution to the AIDS problem. It has become clear that the scientific community needs to focus a lot of its attention on making a vaccine against HIV.

At the end of 1996, David Baltimore was appointed to head a committee within the U.S. National Institute of Health (NIH), charged with the task of making vaccine research more effective. This is an arduous scientific goal, because the virus attacks the immune system, the system we rely on to protect us against infection, and the system that all other vaccines are targeted to induce.

In an effort to get as wide a range of information as possible, the committee started to hold meetings around the United States. It was decided to hold a further session in Europe in order to contact European scientists to understand what was happening in Europe in this regard, and to develop a co-operative spirit with European scientists in the search for an AIDS vaccine. This was the main reason of the agreement between the Juan March Foundation and the NIH to cosponsor this workshop.

A number of scientists who do not work directly on HIV were invited to the meeting, in an attempt to get a very broad understanding of both the immunology and virology of the problem.

During the meeting, recent experiments and ideas for vaccines were discussed; for instance, there was discussion about how vaccines work in animals. Particularly in monkeys there are viruses very much like HIV, and experiments for the design of vaccines that would work in monkeys were presented.

Other alternatives were discussed. Speakers talked about protein vaccines, chemokine activation or chemokines as vaccines. There was a focus on both the production of antibodies and the production of cytotoxic T lymphocyte cells that provide immunity. It seems that a successful vaccine needs to activate both types of immunity.

Many different preparations of protein have been tested, as well as many different vector systems that bring DNA into cells. Experiments with naked DNA and with live attenuated virus were also presented.

As stated before, the attainment of the HIV vaccine is one of the most difficult pending scientific challenges. Nevertheless, meetings like this one will help to devise routes to better know where to go in the future.

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Biochemistry and Molecular Biology of Non-Conventional Yeasts

Organized by
C. Gancedo, J.M. Siverio and J.M. Cregg

(7- 19 July)

Co-sponsored by the Federation of European Biochemical Societies

During many years, yeast has been equated with *Saccharomyces cerevisiae.* In fact, it is one of the most important organisms in the study of the molecular genetics of eukaryotic organisms. The knowledge of the sequence of its whole genome has opened new avenues to the structural and functional study of previously unknown genes. Other biological features that contribute to the usefulness of *Saccharomyces cerevisiae* in research are among others: its rapid growth rate, the easy isolation of mutants, and the high versatility of transformation methods that offer unique advantages in the isolation and characterisation of genes.

However, other yeasts belonging to different genera are gaining importance in research for different reasons. In fact, there are about 700 yeast species recognised now. Those yeasts belonging to genera different from *Saccharomyces* are designated as non-conventional yeasts.

One of the reasons that make non-conventional yeasts interesting is their potential economic importance, basically as cell factories, to produce foreign proteins of commercial value, some chemicals or other industrial aspects. Another one is that among them we found species that are pathogenic to animals. Also some non-conventional yeasts are being useful tools in the study of some basic processes like the biogenesis of organelles. For all these reasons the species that are receiving more attention presently are: *Hansenula, Pichia, Yarrowia, Kluyveromyces, Candida*, and *Zygosaccharomyces*.

Schizosaccharomyces pombe has not been investigated as much as *Saccharomyces cerevisiae* but is the conventional yeast for the study of the cell cycle. In fact it is considered a bridge between conventional an non conventional yeasts. As the rise in nosocomial candidiasis is becoming rampant, *Candida albicans* is being widely studied. *Hansenula, Pichia, Yarrowia,* and *Kluyveromyces* are investigated for their biotechnological uses. *Pichia* and *Yarrowia* are also being used to study basic problems like organelle biosynthesis and control of dimorphism. Species of the yeast genus *Zygosaccharomyces* are of major importance to the food and beverage industries causing spoilage in several products.

Nevertheless, in spite of their importance, basic knowledge on the biochemistry and physiology of these organisms is very poor; only some techniques for the application of molecular biology methods have been developed. Thus, in an effort to get a better understanding of this problem, it was decided to organise a practical course bringing together a group of scientists working in the forefront of research with non-conventional yeasts.

Hopefully courses like this will help to provide both a theoretical and practical background for people interested either in initiating a research with non conventional yeasts or wishing to acquire new skills to tackle new problems.

C. Gancedo, J.M. Siverio and J.M. Cregg

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1997 Symposium:

Biology at the Edge of the Next Century (100th meeting)

Organized by the
Centre for International Meetings on Biology

(12-13 May)

We are witnessing revolutionary changes in the understanding of living processes in all areas of Biology; many questions that had been asked in the past have finally been answered. This centennial meeting was devoted to revise recent findings, and cast a wider look at the way modern Biology is evolving in representative areas that, among others, are at the forefront of critical achievements.

This symposium was divided into four separate sessions, dealing respectively with:

1) the genome structure of humans and important animal models;
2) the convergent and divergent strategies utilized during development;
3) the cell and molecular basis of the immune system;
4) the many facets of modern neuroscience were analyzed.

The main focus of the symposium was the attempt to sketch the future directions in which these fields are moving, setting the stage for how we view and tackle important biological questions in the near future.

Eleven prominent scientists presented recent contributions in their respective fields, trying to identify the significant questions that must be addressed, and the appropriate strategies to approach them.

This symposium was organized to commemorate the 100th meeting organized since 1989, first by the Juan March Foundation directly, and after by the Centre for International Meetings on Biology, that was established and started working in January 1992.

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PARTICIPANTS

The number of participants admitted to this symposium was purposefully much larger than in the regular workshops organized by the Centre, due to the more diverse character of the scheduled presentations, that addressed several different areas of Biology.

208 participants attended this meeting. The Centre directly invited 137 Spanish scientists and 10 foreign scientists. Out of the 65 applications received, 42 Spanish and 19 foreign scientists were also selected to participate.

1997 FELLOWSHIPS

1997 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 1997, 160 of these fellowships were awarded to participants in 12 different meetings. Among these, 83 fellowships were granted to scientists working in Spain, and 77 to scientists working abroad.

XVI 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 in this field. The invited lecturers often take advantage of their visit to Spain to give additional seminars in different laboratories.

In 1997, the XVI lectures series took place, with the general theme of **RNA PROCESSING**. The speakers and topics were as follows:

17 February

WALTER KELLER

University of Basel. Biozentrum
Department of Cell Biology
Basel (Switzerland)

Posttranscriptional processing and editing of messenger RNA precursors.

Introduced by: **Juan Pedro García Ballesta**

Centro de Biología Molecular "Severo Ochoa"
Universidad Autónoma de Madrid

24 February

JOAN A. STEITZ

Yale University School of Medicine
Howard Hughes Medical Institute
New Haven, CT. (USA)

The cell nucleolus: yet another RNA machine.

Introduced by: **Jesús Avila**

Centro de Biología Molecular "Severo Ochoa"
Universidad Autónoma de Madrid

3 March

TOM MANIATIS

Harvard University
Department of Molecular and Cellular Biology
Cambridge, MA. (USA)

Mechanisms of alternative splicing.

Introduced by: **Miguel Vicente**

Centro de Investigaciones Biológicas
Madrid

10 March

PHILLIP A. SHARP

Massachusetts Institute of Technology
Center for Cancer Research
Cambridge, MA. (USA)
1993 Nobel Prize in Physiology or Medicine

RNA splicing, introns and Biology.

Introduced by: **Mariano Esteban**

Centro Nacional de Biotecnología
Madrid

Sessions Open to the Public

In conection with some workshops, prominent invited speakers have given additional lectures in sessions open to the public. In 1997, these were as follows:

During the workshop on **Plant Morphogenesis** (20-22 October):

- **MARC VAN MONTAGU**
  Flanders Interuniversity Institute for Biotechnology
  Department of Genetics
  University of Gent
  Belgium

  Can we and should we modulate plant growth and development?

Introduced by: **José Luis Micol**
División de Genética
Universidad Miguel Hernández
Campus de San Juan, Alicante (Spain)

During the workshop on **Development and Evolution** (3-5 November):

- **GINES MORATA**
  Centro de Biología Molecular "Severo Ochoa"
  CSIC – Universidad Autónoma
  Madrid (Spain)

  Homeobox genes in development and evolution

- **DENIS DUBOULE**
  Department of Zoology and Animal Biology
  Faculty of Sciences
  University of Geneva
  Geneva (Switzerland)

  Genetic control of vertebrate limb development and evolution

Introduced by: **Walter J. Gehring**
Biozentrum
University of Basel
Basel (Switzerland)

Reviews in Scientific Journals

REVIEWS IN SCIENTIFIC JOURNALS

During 1997 the meetings organized by the Centre have been reviewed in the following articles:

Fresno, M., Kopf, M. and Rivas, L. (1997). Cytokines and Infectious Diseases. **Immunology Today 18**: 56-58.
(On the workshop of the same title, held in June, 1996)

Quatrano, R.S.,Barthels, D., Ho, T.H.D. and Pagès, M. (1997). New Insights into ABA-Mediated Processes. **Plant Cell 9**: 470-475.
(On the workshop on *Abscisic Acid Signal Transduction in Plants*, held in October, 1996)

Benkovic, S.J. and Ballesteros, A (1997). Biocatalysts – The Next Generation. **Trends in Biotechnology 15**: 385-386.
(On the workshop on *Novel Biocatalysts*, held in March 1997)

Dickman, S. (1997). Possible New Roles for *HOX* Genes. **Science 278**: 1882-1883.
(On the workshop on *Development and Evolution*, held in November 1997)

Akam, M.(1998). The Yin and Yang of Evo/Devo. **Cell** (In press).
(On the workshop on *Development and Evolution*, held in November 1997)

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.** Centro de Investigaciones Biológicas. Madrid. **D. Chattoraj.** Laboratory of Biochemistry. NIH-NCI. Bethesda. **G. Wagner.** The Swedish University of Agricultural Sciences. Uppsala.
23-25 February	**Mechanisms Involved in Visual Perception**	**A.M. Sillito.** Institute of Ophthalmology. London. **J. Cudeiro.** Departamento de Ciencias de la Salud I. Universidad de A Coruña.
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**	**F. M. Goñi.** Facultad de Ciencias. Universidad del País Vasco. Bilbao. **J.L.R. Arrondo.** 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. Universidad Politécnica de Madrid. **P. Palukaitis.** Scottish Crop Research Institute. Invergowrie, Dundee. **K.J. Oparka.** Scottish Crop Research Institute. Invergowrie, Dundee.
11-13 May	**Cellular Regulatory Mechanisms: Clocks, Choices, Time and Space**	**P. Nurse.** Imperial Cancer Research Fund. London. **S. Moreno.** Instituto de Microbiología Bioquímica. Universidad de Salamanca.
25-27 May	**Wiring the Brain: Mechanisms that Control the Generation of Neural Specificity**	**C. S. Goodman.** University of California, Berkeley. **M. Tessier-Lavigne.** University of California, San Francisco. **F. Bonhoeffer.** Max-Planck-Institut für Entwicklungsbiologie. Tübingen. **R. Gallego.** Instituto de Neurociencias. S. Juan, Alicante.
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	**NO: from Discovery to the Clinic**	**S. Moncada.** The Cruciform Project. University College London. **S. Lamas.** Centro de Investigaciones Biológicas. Madrid.
5-7 October	**Chromatin and DNA Modification: Plant Gene Expression and Silencing**	**T.C. Hall.** IDMB. Texas A & M University. College Station. **A.P. Wolffe.** National Institutes of Health. Bethesda. **R.J. Ferl.** Department of Biotechnology. University of Florida. Gainesville. **M.A. Vega-Palas.** Instituto de Bioquímica Vegetal y Fotosíntesis. Sevilla.
19-21 October	**Transcription Factors in Lymphocyte Development and Function**	**J.M. Redondo.** Hospital de la Princesa. Universidad 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**	**J. Schell.** Max-Planck-Institut für Züchtungsforschung. Köln. **R. Walden.** Max-Planck-Institut für Züchtungsforschung. Köln. **A.F. Tiburcio.** Facultad de Farmacia. Universidad de Barcelona.
30 November/-2 December	**Structure and Mechanisms of Ion Channels**	**J. Lerma.** Instituto Cajal. Madrid. **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.

Index of Personal Names

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

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

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

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

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

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

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

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

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