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José-Antonio Campos-Ortega (1940-2004) and his scientific work - a personal perspective

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ABSTRACT José Antonio Campos-Ortega (1940-2004), a Spanish scientist who became a leading figure in the developmental genetics of the nervous system, spent most of his scientific life in Germany. Nevertheless, he remained deeply rooted in his native country. His thinking, his ambition and his work were driven by scientific, philosophical and historical questions. He started as a neuroanatomist, working first in Valencia, then in Göttingen, Tübingen and Freiburg. He used primates, reptiles, then the house fly and finally *Drosophila* to address the question "How is the brain or the eye structured in order to function?". While in Freiburg, the problem shifted to "How does the nervous system come into being, into form?" Campos-Ortega tried to understand early neurogenesis in *Drosophila* through formal genetics, by identifying relevant genes and studying their genetic interactions. Since he was convinced that not only a single experimental approach could solve a problem as complex as the development of the nervous system, he also included the molecular biological approach when he moved to Cologne, while maintaining a strong focus on anatomy, embryology and genetics. There, he also started to work on the neurogenesis of the zebrafish, using similar concepts and approaches. Throughout his scientific career, he thought, wrote and taught about the evolution of methods and ideas in his field of research. At Campos-Ortega's early death, an unfinished book manuscript was left, entitled "Developmental Genetics. The Path to the Biological Synthesis". Some parts of his introductory overview are included here.

KEY WORDS: *neurogenesis, Drosophila, zebrafish, neurogenic genes, neuroanatomy*

A Spanish introduction to Science

"...but our knowledge is so weak that no philosopher will ever be able to completely explore the nature of even a fly ..." (Aquinas, 1273). Thus reads the introductory quote in José's book on *Drosophila* embryonic development (Campos-Ortega and Hartenstein, 1985). This quote - taken from the Dominican *Doctor angelicus* Thomas de Aquino (1273) - is more than just a spirited, funny motto inserted by an erudite author. It reflects the tension of José's Spanish origins: between rational scientists, medical doctors, liberal agnostics and the religious, catholic bourgeoisie. Campos-Ortega adhered to the former party, but he was highly knowledgeable of the old philosophic-theological and historical wisdom, of course, after seven years in high school with the Dominican Fathers. Those questions remained the essence of José's scientific struggle. The Latin text of Thomas de Aquino continues: ... *unus philosophus fuit triginta annis in solitudine, ut cognosceret naturam apis* (One [scientist] stayed in the solitude of the desert for thirty years, to learn about the nature of a bee). Some months before he died, Thomas had stopped writing, exhausted, tired, perhaps desperate, saying: *Omnia quae scripsi mihi videtur ut palea* (All I have written appears to me like chaff). José Campos-Ortega, in one of his last e-mails, wrote to a friend: *"... you refuse to believe it, but I do have great doubts in an area which is so important to me, in my 'Forscherleben', my life as a researcher. When I think that the illness will end these damned doubts, then this may bring a positive touch to this aspect of my life; ... I was always excessively ambitious... and driven by ambition .... I made mistakes over mistakes. Now I try ... to ignore, to forget my 'Forscherleben'."*

José Antonio Campos-Ortega was born on August 22, 1940, as the second son of Arturo Campos Marques and Maria de la Conception Ortega Perez de los Cobos, in a medical doctor's family in Valencia. Already at the age of four he entered the

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Fig. 1. José's student passport from 1957 from the University of Valencia.

elementary school *Colegio del Sagrado Corazón de Jesús*, where he stayed for six years, followed by another seven years at the above-mentioned Dominican high school in Valencia. In 1957 he registered at the University of Valencia (Fig. 1). Having thought that philosophy would not easily allow him to earn a living, he started to study natural sciences for one year. After that he switched and studied medicine until 1963. Already as a young student, 1959-63, he did practical research work on the histology of nerve endings in a laboratory of the Valencia School of Medicine. This institute was under the directorship of Juan José Barcia Goyanes (1901-2003), Professor of Anatomy at the Instituto Cajal. This institute was one of the oldest centres for a research area which is now known as neurobiology. And there was another – strong – imprint on José's decision. During 1883-1887, the most famous brain and neuroanatomist Santiago Ramón y Cajal had worked as Professor of Anatomy in José's hometown Valencia. This towering figure, who was awarded the Nobel Prize for Physiology and Medicine in 1906, certainly left an early mark on José's scientific ambition. (For more details and for a vivid description of the Valencia situation at that time, see the article by Roberto Marco Cuéllar, a friend and fellow student of José (Marco, 2006)).

Starting in 1963, Campos-Ortega worked in a small group, which much later developed into the Institute for the History of Medicine. Under the guidance of José María López Piñero they performed studies on the early Spanish school of histology, specifically on the Spanish predecessors of Ramon y Cajal. (We will see further ahead that history of science remained a *Leitmotiv* throughout José's life). He was co-author of two papers (Terrada Ferrandis *et al.*, 1963a, Terrada Ferrandis *et al.*, 1963b), which were presented on the 1st Spanish Congress of the History of Medicine. In December 1963 he received the "Peregrin Casanova" prize, which was awarded every year to the best student in the field of anatomy. From 1964-66, José Campos-Ortega worked on his thesis at the 2nd chair of Anatomy, held by Prof. José María Smith Agreda. José studied the cyto- and myeloarchitecture of the diencephalon of some reptiles. He graduated in 1967 as a Doctor of Medicine and Surgery at the University of Valencia. Roberto Marco describes how Campos-Ortega did his neuroanatomical research in the framework of the Spanish School, using brains of all sorts of animals: laboratory rats, guppy fishes kept in a glass bowl at home, bats - the heraldic animal of Valencia -, snakes, lizards, small turtles and the chelonid *Emys orbicularis*, to mention just a few (Marco, 2006). The results of these studies were the basis of his thesis (Campos-Ortega, 1966) and were published in Spanish, in Spanish Journals.

In Valencia, José had remained close to his home and family, in an old and venerable neurohistological/anatomical tradition, where both his grandfather and father were running medical practices. In neurohistology, Barcia Goyanes, a "distant" student of Ramón y Cajal, had many obligations outside the lab, first as dean and later as *Rector Magnificus*. For some years, José's real advisor, e.g. for the classical silver impregnation technique, was a more advanced fellow student, Carlos (Karl) Meller, of German descent. When Meller left Spain in 1961, José and his friends were left alone. José felt that he had to leave Valencia as well and to start a serious research career elsewhere. Carlos Meller had taken a position at a new Department of Histology and Neuroanatomy in Göttingen, under a new director, the neurophysiologist Paul Glees. In 1965 José received a letter offering him an assistantship in this place. In the same year, he married Maria Teresa Lleó Alama, and in 1966, his first son, Arturo, was born in Valencia.

The years in Göttingen and Tübingen: anatomy of the nervous system

José Campos-Ortega's work in Göttingen (1966-1970) concentrated on the description of the central connections in the visual system of mammals, in particular primates. His interest was focused on neuroanatomical structures as the basis for signalling functions, and not (yet) on the ontogenetic development of the neural patterns. When he arrived in Germany, his Spanish degree was not immediately accepted. Impatient as he was, and not willing to struggle with German bureaucracy, he produced another thesis within a very short period of time ("Cytoarchitektonische Untersuchungen am Zwischenhirn des Halbaffen *Galago crassicaudatus*") and obtained the German *Doktortitel*, making him *Herr Dr. Dr. med. Campos-Ortega.* His daughter Teresa was born during the time in Göttingen, and his third child, Nicolas, in December 1970, already in Tübingen.

In the *Institut für Histologie und Neuroanatomie,* José performed all the duties and jobs of a German *Wissenschaftliche Assistent*, as documented in the official *Zeugnis* (certification), written at the end of his stay in 1970. Only about 27 years old, he was *Assistent* in lab courses for students in their first year, he supervised and advised the work of two doctoral students, he collaborated in a project producing a stereotaxic atlas of the *Pavio* brain, and he was principal investigator of a project funded in the frame of the Sonderforschungsbereich 33 "*Nervensystem und Information*". The *Zeugnis* states that Campos-Ortega achieved international reputation "… *durch beispielhaften unermüdlichen Einsatz einschlieβlich an Sonn- und Feiertagen"* (by exemplary and untiring efforts, even on Sundays and holidays).

His research covered light and electron microscopy (Fig. 2), neurocytology and histology. He used the silver impregnation technique, improved by Prof. Glees, which allowed one to trace axon degeneration, induced by an experimental lesion. Thus he could analyse in detail where the axons, starting from a defined region of the brain, project. Several papers resulted from the collaboration with W.R. Hayhow, a visiting Professor from Australia, studying neural connections in the central optical system in mammals, with the focus on primates. In the last paper of this series (Campos-Ortega and Hayhow, 1972), the authors proposed a functional neuroanatomical scheme, representing parts of this (too) big and complex brain, with connections between visual cortex and thalamus.

After some attempts to return to Spain, he decided in 1970 to stay for a few more years in Germany. He moved to the *Max-Planck-Institut für Biologische Kybernetik* in Tübingen as a research scientist in the *Abteilung* (Department) of Valentino Braitenberg. In April 1970, he wrote to a friend: "*Aquí* [in Tübingen] *empezaré a trabajar el 1 de Julio de ese año, y mi intención es permanecer en ese instituto por algún tiempo, 3 ó 4 años. Mi tema de trabajo va a ser la estructura del aparato óptico de los dipteros. …. Esa casa se dedica integramente, con neurofisiólogos, psicologos, otros morfólogos aparte de mi, a esa tema. Se mascan ganglios opticos de la mosca, literalmente, en el ambiente. Creo que ahí encontraré la orientación y el apoyo que estoy buscando desde hace tiempo*." (I will start working here [in Tübingen] on July 1st of this year, and I intend to stay in this institute for some time, 3 or 4 years. My topic will be the structure of the optic apparatus of dipterans. This "house" is dedicated to this topic in an integrated way, with neurophysiologists, psychologists and other morphologists besides me. Literally, optic ganglia of the housefly are being "chewed" there. I believe that I will find there the advice and the support, which, for quite some time, I have been looking for). As Hartenstein pointed out (Hartenstein, 2006), one of the motifs was – as it was for others in that period – to leave the complex vertebrate brain and to switch to "simpler" systems, e.g. to the visual system of an invertebrate, the fly. It was the hope that this system would allow an understanding of neural connections, for example those between the eye and the optic lobe, at the level of individual axons.

Much of the activity in the group in Tübingen concerned visually controlled motor patterns in the house fly *Musca domestica*. Campos-Ortega worked for several years in Braitenberg's laboratory and made many discoveries on the microcircuitry of the optic lobe. He demonstrated, for example, the interneuronal network in the lamina at the single cell level (Campos-Ortega and Strausfeld, 1972). This paper and the subsequent review (Strausfeld and Campos-Ortega, 1972) have contributed much to the famous, canonical insect brain atlas (Strausfeld, 1976).

Fig. 2. José (left, next to the microscope) during an electron microscopic course held in Eindhoven (1971).

Genetics in Freiburg: the fanaticism of formal genetics

In 1973, José Campos-Ortega was offered a tenure position as *Professor und Wissenschaftlicher Rat* at the University of Freiburg i.Br., at the *Institut Biologie III (Genetik, Molekularbiologie und Biophysik).* Only in one of the last meetings, the search committee recognised his qualities and changed the list. He had no *Habilitation*, but in an un-bureaucratic move, the Freiburg Biology arranged a retroactive procedure (*Nach-Habilitation*), which allowed José to start working in Freiburg in 1973. Creative activity, outspoken comments and criticisms, emotional intelligence and his interest in the work of other groups – if interesting– made an immediate impression.

"He moved to *Drosophila* ", i.e. from the bigger house fly to the smaller, but genetically accessible fruit fly. This move sounds an easy one, but for somebody who had not got any major education in genetics, as was the case with Campos-Ortega, this really meant a change in methodology and concepts. At the same time, this move came as a surprise to his colleagues, since they expected him to work on neuroanatomy or biophysics, for which he had been hired.

During the first years in Freiburg, José's group studied fine structure and clonal development within the *Drosophila* eye and optic lobe, using the mutation *sevenless* among others (Campos-Ortega *et al.,* 1979). Soon these anatomical studies were superseded by neurogenetics, or more precisely, by developmental genetics of (early) neurogenesis. The focus shifted from "How is the brain or the eye structured in order to function?" to "How does the nervous system come into being, into form?" This was the beginning of a fierce intellectual struggle to understand the formal genetics relevant to neurogenesis, and to understand it by indirect reasoning, at least as long as no molecules were known. The research of the group was exciting, full of stress and very, very difficult. Colleagues that attended common lab seminars sometimes cursed the hour-long fights about epistasy and inhibition of inhibition, and then this obstinate *Notch* with or without

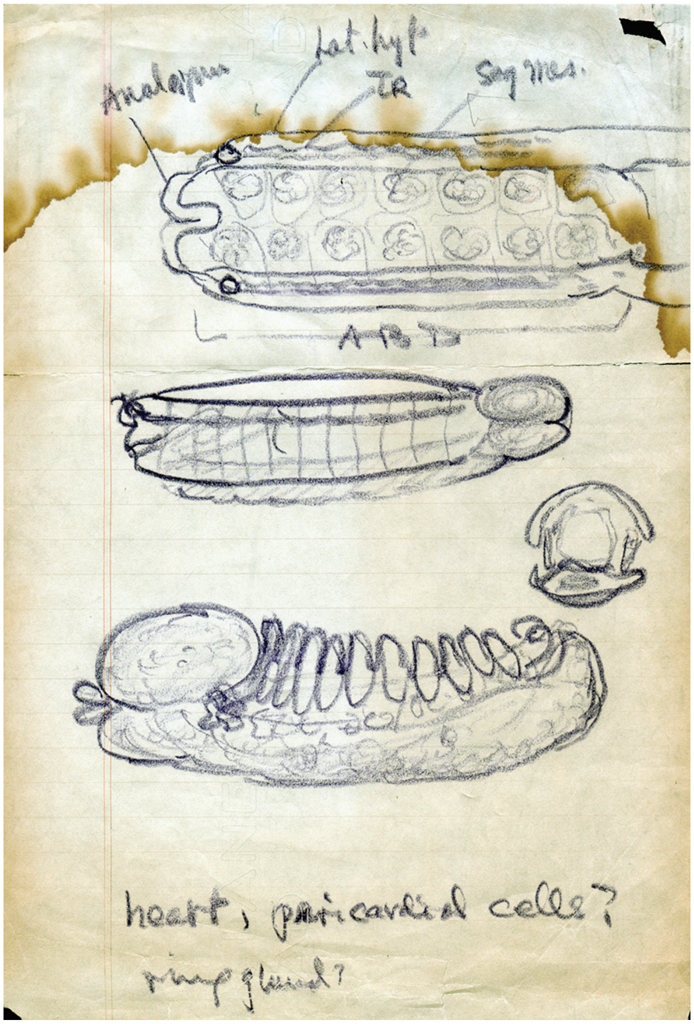

Fig. 3. *Notch* mutant embryo. *This picture, hand-drawn by Donald F. Poulson, was hanging behind José's desk. Top and middle: ventral views; bottom: side view. The side view shows the hyperplasia of the brain (left) and the ventral neurogenic ectoderm.*

Enhancer of split … and on top of it, vociferous arguments about Ed Lewis' incomprehensible *bithorax-Ultrabithorax*-mutants (Lewis, 1978) were discussed to the highest pitch. At a certain point, a time-out was decided: three weeks peace without any *Drosophila.* With today's molecular information, very few can still understand the thrill of formal genetic reasoning. Volker Hartenstein, one of the early students in the Freiburg lab and co-author of the important book on the *Drosophila* embryo (Campos-Ortega and Hartenstein, 1985), provided a detailed review of José's research at that time, with a profound interpretation of ideas and techniques (Hartenstein, 2006). Therefore, we will only highlight some of the aspects.

Developmental studies with genetic methods had only very few precursors. One of the first papers was that of Donald F. Poulson (Poulson, 1940), who used X-chromosomal deficiencies to study the embryonic development of *Drosophila*. The paper starts: "*The problem of how the genes act in development may be approached in several ways, more or less indirect. The effects of the dosage of genes on the end character, or upon the development morphology, as well as the differences in the effects of allelomorphs may be of the nature of cell size, shape, number, or pattern, or rate of developmental reactions.... Another, and more direct approach is through the study of the effects of the absence of certain genes*." This paper gives the first phenotypic description of embryos mutant for *Notch*, a gene discovered by Otto L. Mohr (Mohr, 1919), which was to become one of the best known *Drosophila* genes later on. A picture showing a *Notch* mutant embryo, hand-drawn by Donald F. Poulson, hung behind José's desk (Fig. 3). *Notch* has not only turned out to be involved in many developmental processes in the fly, but the Notch signalling pathway also plays an important role in humans. Mutations in human *Notch* are associated with a variety of diseases, such as hereditary cardiovascular disorders, leukaemia and cancer formation. This indicates that it also participates in the regulation of several developmental processes in human, such as stem cell self-renewal, proliferation, specification of cell fate or apoptosis (Gridley, 2003; Hofmann and Iruela-Arispe, 2007; Hurlbut *et al.*, 2007).

In the late 1960s, more mutant phenotypes had been characterised in *Drosophila* embryos (see Wright, (1970) for review), demonstrating the power of genetic screens. During the following years, several groups working on the developmental genetics of *Drosophila* regularly met (Fig. 4 shows a number of important players in the field). Their discussions dealt, among others, with the design of genetic screens and their implications, the results achieved from mutant clones obtained by X ray-induced somatic recombination, or the significance at borders in gynandromorphs. To this group it was very obvious that the genetic approach is the ideal way to dissect the complexity of developmental biology. In other words, as phrased by Antonio García-Bellido at the opening remarks made at a Symposium in India: *"In my view, the best instrument to see order in this jungle is genetics. Genetics is precisely a science of interaction. ……. It could help us as the Ariadna's thread to not get lost in the labyrinth"* (García-Bellido, 1980). Antonio García-Bellido, a leading figure in the Genetics and Developmental Biology of *Drosophila* in Spain, established an impressive school of scientists in Madrid, which made major contributions in the field until today [see Ghysen (2009) and also the Special Issue of the *Int. J. Dev. Biol.* "Developmental Genetics of *Drosophila* ", Vol. 42, No.3, (1998), published in recognition of Antonio's contribution].

And there was a microscopic technique that became an important tool for the Campos-Ortega group and for others as well, which made it possible to study embryonic phenotypes: a technique, simple, old-fashioned and, most important, fast, in which fly embryos were fixed and stained with Fuchsin and observed thereafter, not in sections, but in whole mounts (Zalokar and Erk, 1977). This procedure gives an intense staining of the cell nuclei, more intense than achieved with Feulgen, and nearly no background of the cytoplasm (Fig. 5). This technique, combined with screening deficiencies that covered a larger portion of the genome (which would be called a "genome-wide approach" today) allowed the identification of genes involved in neural development by their mutant phenotypes revealed by Fuchsin staining. By this technique, a region at the tip of the X-chromosome, the *achaete-scute* complex *(AS-C)*, was found to be essential for normal neurogenesis in the embryo (Jiménez and Campos-Ortega, 1979) (Fig. 6). A central finding for dissecting the genetics of early neurogenesis was the characterisation of a group of genes, the

Fig. 4. The "*Drosophila* Mafia Meeting" in 1980 at Willington, U.K. *From left to right: Gary Struhl, Lucas Sanchez, Andreas Dübendorfer, Mike Wilcox, Ginés Morata, Danny Brower, Pedro Ripoll, Peter Lawrence, Rolf Nöthiger, Ruth Lehmann, Gerd Jürgens (partly hidden), José Campos-Ortega, Trudi Schüpbach, Christiane Nüsslein-Volhard, Eric Wieschaus, Fernando Jiménez.*

so-called neurogenic genes, which restrict the number of neuroblasts in the neurogenic ectoderm, thus allowing the development of the epidermis. One of them was the famous *Notch.* Additional neurogenic genes were identified, such as *big brain, Delta, master mind* and *neuralised*, which all cause hyperplasia of the embryonic nervous system, accompanied by a hypoplasia of the epidermal sheath (Lehmann *et al.,* 1981). The latter paper ends with the following sentence: "*It is still an open question, as to whether or not these loci are functionally linked*". Today's knowledge, obtained by the molecular analysis of these genes convincingly underscores the power of the genetic approach. José was also the first to demonstrate that *Notch* and *master mind* have, in addition to a zygotic component, a maternal component of gene expression. This could be achieved by making use of the dominant female sterile mutations, which were discovered only shortly before (Wieschaus *et al.,* 1981), in order to detect mosaics in the germ line (Jiménez and Campos-Ortega, 1982). This technique has become a standard technique in fly genetics.

Using another approach, the first neuroblast map showed that these cells, which are the precursors of the ventral nerve cord, were produced in several waves, and not in all regions of the ectoderm, but only ventrally near the midline (Hartenstein and Campos-Ortega, 1984). Two important aspects of this map have to be highlighted: first, that neuroblasts do not segregate all at once, but arise in distinct generations, or waves; and second, that neuroblasts and epidermoblasts emerge from the same region in the ectoderm, namely from the entire ventral ectoderm. This, and the observation that only a certain portion of the ectoderm becomes neuralised upon the loss of neurogenic genes led José to analyse the cause for this regional restriction. He could demonstrate that genes controlling the patterning along the dorsal-ventral axis, such as *dorsal,* are epistatic to *Notch* (Campos-Ortega, 1983). In *Notch* mutants, only the ventral half of the ectoderm turns completely into neural tissue, whereas only a narrow band of ectoderm around the ventral midline produces neuroblasts when *dorsal* function is simultaneously reduced. He concluded from the results that *dorsal* acts first, i.e. it is epistatic to *Notch*, in that it patterns the ectoderm along the dorsal-ventral axis into a non-neurogenic dorsal and a neurogenic ventral half, and that the neurogenic genes only act in the latter. Or, to cite his conclusion "*neurogenic abilities of ectodermal cells depend on the activity of genes controlling the embryonic dorso-ventral patterning rather than on the position of the cell.*" However, he also concluded from these results that the neurogenic ability of the ventral ectoderm is not uniform, but graded, an observation that was confirmed a few years later by elegant transplantation experiments of labelled cells (Technau and Campos-Ortega, 1987).

José's work was recognised and honoured, for example in 1977, when he became a fellow of the European Molecular Biology Organization (EMBO) and later a member of the EMBO council, or in 1986, when he became a corresponding member of the Spanish Academy of Sciences.

José not only pushed forward his own research, but he also became involved in another project, namely as a colour-blind (protanope), patient and intelligent test object. While in Freiburg, and later in Cologne, even during the last months of his life, he

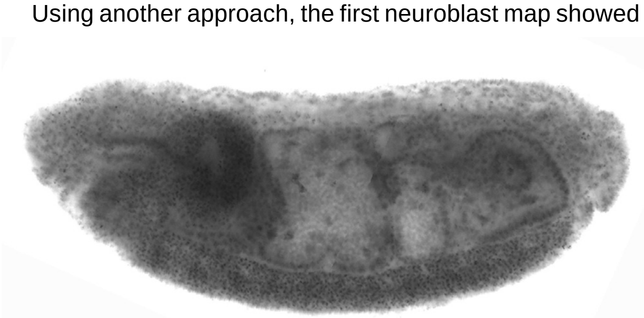

Fig. 5 (Above). A wild-type stage 16 embryo stained with fuchsin. *Anterior is left, dorsal up. Note the prominent ventral nerve cord.*

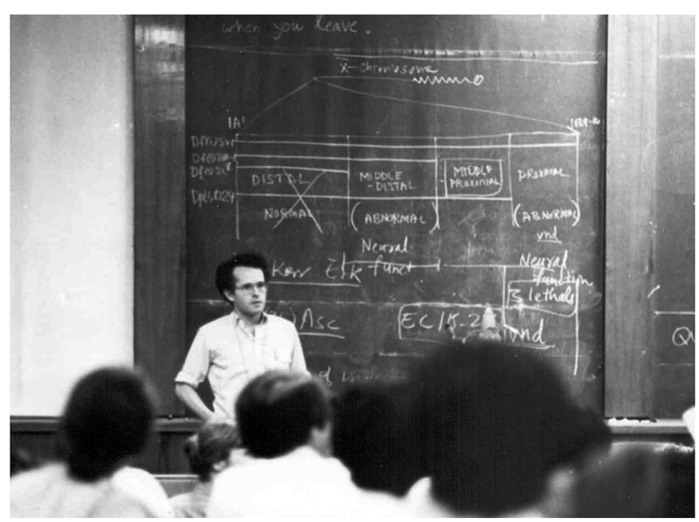

Fig. 6 (Right). José giving a lecture about the AS-C complex. *The drawing on the blackboard depicts the tip of the X-chromosome.*

Fig. 7. Picture taken from a Black Forest hiking tour of the Institut Biologie III in the autumn of 1979.

helped to answer the question, how red-green colour blind persons use their "red" and "green" subjective colour percepts. They do have these percepts, and they use them meaningfully (Wachtler *et al.,* 2004).

José also very actively participated in the life of the Institute. From 1977 to 1980 he was elected *Direktor des Instituts Biologie III*, which was less of an honour than a hard job. He managed it with dedication and success – even when he had to go through a great crisis of his life. Memorable were also the hikes and fieldtrips of the Institute, organised by the passionate *Wanderer* that he was (Fig. 7). And he was an enthusiastic teacher, particularly when he met enthusiastic students. He not only gave lectures in his field, but in Freiburg he resumed his earlier "hobby" and gave lectures on the history of genetics, developmental biology and evolution (see ahead). There is one criterion, in addition to scientific excellence and originality, to judge a professor's quality: whether he produces – or rather: whether he allows – students and collaborators to become leaders in their scientific field. An incredibly long and most impressive list of names can be found as authors of the publications from José's Freiburg group.

And suddenly, in 1982, José Campos-Ortega left Freiburg to move to Cologne. The friends in Freiburg still cannot believe that he had been there only nine years. The impact he left was such as if he had been there for decades.

Developmental genetics in Cologne: *Drosophila* and zebrafish

Why leave Freiburg, situated in a lovely region of Germany, and move to Cologne, a huge city further north? Two points may have been decisive: one related to scientific progress made at that time, and the other related to José's personality.

In the 1970s, advances in molecular biology made it possible to isolate continuous genomic DNA of *Drosophila* by "chromosomal walking" from libraries of overlapping bacteriophage clones and to map it to a specific chromosomal region by *in-situ* hybridisations to polytene chromosomes (Wensink *et al.,* 1974). This, in turn, allowed the positional cloning of the first *Drosophila* gene, *Ultrabithorax*, in 1979, followed shortly later by the cloning of the *Antennapedia*-complex (see Rubin and Lewis (2000) for review). The molecular characterisation of these gene complexes was facilitated by the fact that both of them had been extensively studied by classical genetics, which allowed correlating the genetic and molecular maps. The molecular approach opened a completely new perspective on how to unravel the function of a gene. Shortly after that, *Notch* was cloned by two groups (Artavanis-Tsakonas *et al.*, 1983; Kidd *et al.*, 1983).

In 1982, Michael Levine, at that time working at the Biozentrum Basel in the group of Walter Gehring, came for a seminar to the University of Freiburg. In his talk, he presented data on the spatial expression pattern of the homeotic gene *Antennapedia* by *in situ* hybridisation of radioactively labelled probes to sections of *Drosophila* embryos (Hafen *et al.,* 1983). José, who was in the audience, was thrilled by these results and immediately recognised the power provided by the novel molecular techniques. Now one could really see a gene "in action", and the pattern of expression correlated surprisingly well with its function as derived from the mutant phenotype! José, who was always convinced that the use of only a single method could not resolve a scientific question, decided to include the molecular approach in his scientific program, despite the fact that he himself had never received any training in molecular biology. So, the offer to move to Cologne came just in time, since this allowed the expansion of his group, and the addition of molecular studies to genetics, anatomy and embryology. He was convinced that the genetic network of the neurogenic genes which he had tried to understand by studying the phenotypes, was based on a molecular network, which to uncover was a challenge that he was ready to accept. From this point of view, it was some kind of a disappointment when he saw the first result of the spatial expression of *Notch*, analysed in collaboration with Michael Akam. In a letter from February 1984, Michael wrote: "*I still do not know whether I really believe them* (the first results*), but the observation was that the Notch clone and the excised fragment both appeared to label all cells in the embryo, whereas.... the bithorax plasmid gave only the expected pattern of labelling. ......, but at present it seems most likely that the Notch RNA is not localised to only a few cells.*"

With the move to Cologne, to the *Institut für Entwicklungsphysiologie* (later: *Entwicklungsbiologie*), work on the neurogenic genes and their function in the development of the nervous system of *Drosophila* got an additional facet, and an ambitious one as well, since the group set off to clone *Delta*, *master mind*, *Enhancer of split* and *big brain.* At this time, *Flybase* did not exist, and cloning of a gene meant positional cloning, which required an entry into the genome as close as possible to the gene of interest. And this was difficult, given that at that time only very few molecular probes were available. The successful molecular analysis of *master mind*, *Delta* and *Enhancer of split* (which turned out to be a gene complex, which could finally explain many of the previous genetic results) was published in the following years (Klämbt *et al.*, 1989; Knust *et al.*, 1987; Vässin *et al.*, 1987; Weigel *et al.*, 1987).

It was in 1984 that José accepted an invitation by Enrique Cerdá-Olmedo to present his data for the first time in Spain, in Seville, on the occasion of a course entitled *"Los bisnietos de Mendel"* (The great-grandsons of Mendel). In his reply to the invitation he wrote: "*Gracias por tu invitación, que acepto gustoso – mas aún teniendo en cuenta que este será el primer seminario en castellano de mi carrera. Además de poder contaros lo que* *hacemos, tu invitación me da la oportunidad de visitar otra vez España, donde no he estado durante los últimos cinco años*." (Thank you for the invitation, which I accept with pleasure– even more if one takes into account that this will be the first seminar in my career presented in Spanish. Besides telling you what we are doing here, your invitation provides me with the opportunity to visit Spain once again, something I have not done for the last five years). The title of his talk was "Desarollo del sistema nervioso de *Drosophila* " (The development of the *Drosophila* nervous system). He presented the different approaches being used in his group, which were aimed at understanding how the nervous system develops in the early embryo. He closed his talk as follows: *"Ya he mencionado que el problema de la regulacion genetica es el mas atractivo desde el punto de vista intelectual, pero desgraciadamente también el mas complejo".* (As I have already mentioned, the problem of genetic regulation is the most attractive one from an intellectual point of view, but unfortunately also the most complex). Coming back from Spain, he wrote to Enrique: *"Me gustó mucho* [la participation en el curso], *una gran experiencia – que por supuesto quisiera repetir a la primera opportunidad. Esa 'primera oportunidad' bien pudiera ser la reunion informal de biologos del desarrollo hispanohablantes."* (I very much enjoyed participating in the course, a great experience – which certainly should be repeated when the opportunity arises. This 'next occasion' could well be an informal meeting of Spanish speaking developmental biologists). And in fact, from this time on, he visited Spain more often and his relation to Spanish developmental biologists became closer, which was manifested by the fact that he became a member in the evaluation committee of the *Fundación* Juan March. This foundation supported, among others, various famous meetings in Developmental Biology, which very often took place in beautiful places in Spain. José participated in several of these (Fig. 8).

From 1987 to 2003, the *Fundación* Juan March also edited a journal, *Saber leer* (knowing how to read), with critical comments on books recently published in all scientific areas. From 1991 to 2003, José regularly contributed comments on various books, especially on books dealing with historical aspects of developmental biology or genetics, among them works about Martin Heinrich Rathke or Hans Spemann [see the *Int. J. Dev. Biol.* Special Issue entitled The Spemann-Mangold Organizer; in particular, the 2001 re-edition of the original seminal paper by Hans Spemann and Hilde Mangold (Int. J. Dev. Biol. 45: 13-38) and also, Sander and Faessler, 2001], or "The history of the gene" by Evelyn Fox Keller. By writing these comments, he could perfectly make use of his awareness of the perspectives of these scientific areas and his sense for the historical connections between them (see ahead).

The biggest effort José undertook to strengthen his relation to Spain was when he became involved in the foundation and organisation of a research institute for molecular and developmental biology in Sevilla, together with Enrique Cerdá-Olmedo, Miguel Beato, Manuel Perucho and José Lopéz Barneo. This institute would have allowed him to transfer part of his scientific activity to Spain, and he was looking forward to this possibility. Unfortunately, due to administrative and political reasons, the project in its initial design was never launched. Since 2003, the building that could have hosted the original institute, accommodates the *Centro Andaluz de Biología del Desarrollo*, CABD (Andalusian Centre for Developmental Biology), an institute jointly funded by the Spanish Research Council CSIC, the Andalusian Government and the University *Pablo de Olavide* of Seville. The building, which houses the CABD today, is now called *Edificio Number 20 'José Campos-Ortega'.*

The scientific life in the institute in Cologne was characterised by a lively atmosphere, imprinted by José's never ending curiosity, his ambition to understand the mechanisms of early neurogenesis in *Drosophila* and his ability to put together people working in different disciplines, such as embryology, genetics and molecular biology, to solve the problem. The "Green Book" (Campos-Ortega and Hartenstein, 1985) was published just in time to help people who had mainly been trained in molecular biology to understand the development of the *Drosophila* embryo and, even more important, to allow the interpretation of the expression patterns of the genes they worked on.

In October 1987, José, who had worked for more than a decade on *Drosophila* neurogenesis, wrote to a friend: "*I intend to start working with zebrafish within this winter semester. … My intention is, for this next year, to become familiarised with the embryogenesis of the fish and to try to reproduce Streisinger's and your results at producing homozygotes and lethals. If all works out as well as I expect, I shall then consider moving, say 2/3 of my laboratory to zebrafish work*". So fish tanks were installed in the institute, and the "*Drosophilists"* realised the efforts it took to establish a new system, more or less from scratch. José, again, used a multidisciplinary approach to unravel neurogenesis in vertebrates, the organisms on which he had initiated his career, using his knowledge obtained while working on flies. His first paper on zebrafish was published in 1992 (Bayer and Campos-Ortega, 1992), where the enhancer trap technique, which had been established in flies only a few years before (O'Kane and Gehring, 1987), was adopted to zebrafish. This method allowed isolating cell-specific reporter lines. He and his collaborators in Cologne isolated the orthologues of several fly neurogenic genes,

Fig. 8. Picture taken at the 100th symposium organised by the *Fundación* Juan March in May 1997 on "Biology at the edge of the next century". *Back row, from left to right: José Campos-Ortega, Miguel Beato, Gregory Gasic, Margarita Salas, Eric Kandel, Thomas M. Jessel. Front row, from left to right: Antonio García-Bellido, César Milstein, Gerry Rubin, Sidney Brenner, Carlos Martínez Alonso.*

among them members of the *Her (Hairy/Enhancer of split-related), Delta* and *Notch* families, and analysed their expression patterns and aspects of their function. They studied the cell lineages and the morphogenetic movements during development of the neural tube, and they established the Gal4/UAS system in the fish (Scheer and Campos-Ortega, 1999), which had turned out to be extremely helpful in the study of gene functions in the fly. And finally, his research turned (back) to cell biology when the group studied spindle orientation in the different stages of zebrafish neurogenesis (Geldmacher-Voss *et al.,* 2003), thus providing an explanation of the bilateral distribution of the progeny of individual cells (Fig. 9) (Papan and Campos-Ortega, 1999).

Throughout the time in Cologne, José maintained strong relations with friends and the scientific community in Spain. To recognise José's contribution to the field and to perpetuate the relation between the developmental biologists of Spain and Germany, the German Society of Developmental Biology has laid the basis for a fund, which will serve in the future to finance the *José Campos-Ortega Award*. This prize will be awarded to young, outstanding scientists from Germany or Spain for excellent scientific work in the field of developmental biology. The prize will be awarded on the occasion of the meetings of the German Society of Developmental Biology.

But certainly, the personally most intense encounter that José experienced with Spain was on the *Camino de Santiago* pilgrim's trail. In November 1998, José and Michael Bate walked about 800 km from Roncesvalles in the Pyrenees (in Navarra) to Santiago de Compostela (in Galicia) (Fig.10).

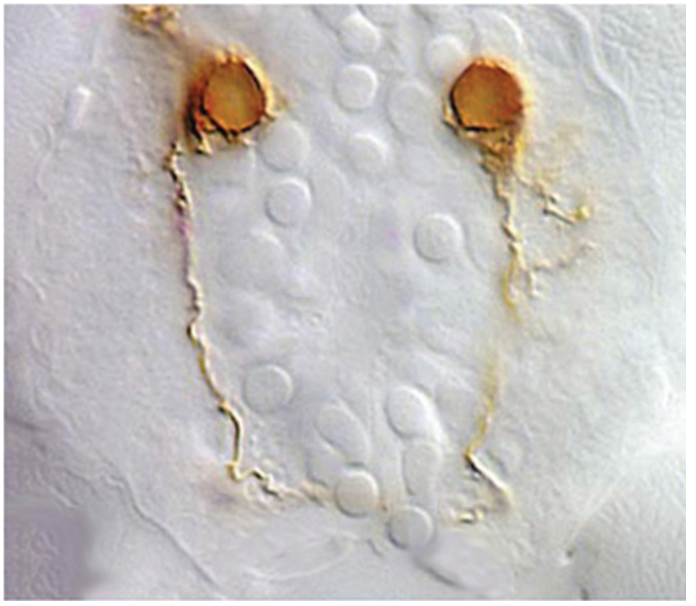

Fig. 9. Cross-section of the nerve cord of a clone showing bilateral symmetry. *The clone was obtained after injection of fluorescein-dextran into a single cell of the neural plate region of a two-somite stage embryo. After another 3.5 days of development, embryos were fixed and stained with an anti-fluorescein antibody. Modified from Papan and Campos-Ortega (1999).*

A history of developmental genetics

José knew about the value of a historical understanding of one's own research. Throughout his scientific career, he thought, wrote and taught about the evolution of methods and ideas in histology, neuroanatomy and developmental genetics: a *Leitmotiv* from Valencia via Freiburg, to his last months in Cologne. His excellent monograph on fly embryonic development (Campos-Ortega and Hartenstein, 1985) could not have been written without his awareness and appreciation of the "old" *Drosophila* literature, in particular without the nearly forgotten work by Donald F. Poulson, a student of Alfred H. Sturtevant, who had applied genetics to study development (Poulson, 1937).

As a very young student, José contributed to the analysis of early Spanish histology, or more precisely, of Spanish neuroanatomy (Terrada Ferrandis *et al.*, 1963a; Terrada Ferrandis *et al.*, 1963b) (see above). The historical description shows that the splendid, original and pioneering work of the great Ramón y Cajal did not come out of a void. He had precursors in his own country concerning theory as well as techniques.

When in Freiburg, José taught a lecture course for several years, together with Rudi Hausmann, Rainer Hertel and Hans Kössel, on the "History of Genetics and Evolution". There were only very few students, perhaps three more than professors, who visited these lectures. Goethe's morphological and anatomical studies were one of José's favourite topics, as well as the *Pariser Akademiestreit,* i.e. the *"Bauplan"* controversy between Étienne Geoffroy Saint-Hilaire (1722-1844) and George Cuvier (1769-1832). The latter could be proven wrong by recent molecular data on the homeobox (Nübler-Jung and Arendt, 1994). José and his audience enjoyed Goethe's slander (to Soret on Feb. 3, 1830; see in Eckermann 1999): *"Cuvier ... besitzt fast gar keine Philosophie"* (Cuvier... has almost zero philosophy). It became a household quote to characterise certain colleagues.

One take-home lesson of the lectures was that considering history as a progressive split and specialisation of research areas is a one-sided view, if not a wrong one. Once in a while there is also a coming together of different guilds, a fusion, a synthesis marking the great leaps forward. Examples are the New Synthesis of the Darwinian evolutionary selection theory and Mendelian genetics, the fusion of cytology and formal genetics to produce the chromosome theory of inheritance, or the fusion of genetics with biochemistry.

As mentioned above, between 1991 and 2003 José regularly wrote comments on scientific books for the journal *Saber leer*, edited by the *Fundación* March. In one article, published in 1998 on *'Hans Spemann y la Biología del Desarrollo'* (Hans Spemann and Developmental Biology), he discussed what was to become a major topic of the book he planned to write, namely *"La síntesis de las disciplinas biológicas"* (The synthesis of the biological disciplines). He wrote about the split between genetics and developmental biology, and about the fusion between the two disciplines as a major achievement in the Biology of the 20th century. But José also reasoned that this split and the initial separation of the two disciplines had actually favoured progress, as he concluded in one of his essays: *"Como en el caso de Morgan y la Genética, también en el de Spemann, cabe pensar que sus logros científicos hubieran sido menores si, junto al desarollo de tritones y ranas, hubiera pretendido también estudiar los mecanismos de transmisión de sus caracteres hereditarios".* (As in the case of Morgan and Genetics, in the case of Spemann, one could similarly imagine that his scientific success would have been smaller if, together with the development of newts and frogs, he had also tried to study the mechanisms of the transmission of their genetic traits) (Campos-Ortega, 1998).

In the last months of his life, in Cologne, José Campos-Ortega worked on a science history book with the working title “Developmental Genetics. The Path to the Biological Synthesis.” He wanted to show that over a short period of time in the 1970s and 1980s, Mendelian genetics - previously mainly transmission genetics with mapping, replication, mutation - came together (in a “synthesis”) with ‘older’ developmental biology, thereby not only providing a theoretical framework, but also new and precise techniques. José’s research group was a player in this explosive period, with *Drosophila* at the focus of attention. In his fragmentary manuscript, Campos-Ortega stressed that the creative, pioneering, fast, new research of developmental genetics did not come out of a void. It had precursors concerning theory as well as methodology. Some excerpts (with minor corrections of the English) from José’s “Introduction” shall give an idea of his planned book:

Campos-Ortega: "Developmental Genetics. The Path to the Biological Synthesis"

"... The main consequence of developmental genetics, while transforming developmental biology, was the achievement - in the very short time span of about 30 years - of a kind of Biological Synthesis, … first in the territory of developmental biology, to be followed by that in bio-medical research. ……….. Researchers of animal and - with a short delay - also of plant development had come to the conclusion that gene function includes providing molecular materials required for the construction of an embryo, and that, on the other hand, the instructions required to steer those molecules in order to construct an embryo, are also encoded in the genes. This conviction was followed soon by the discovery that genes possess phylogenetic conservation, both structurally and functionally. ….

Why this book and why should I have written it? I belong to a group of researchers who lived in the time-span of development of developmental genetics and who made Drosophila and developmental genetics the object of their professional work. Therefore, each member of that group of Drosophila researchers is personally in good conditions to write this book. In any event, [this] group of researchers … is particularly important in the present discussion because they contributed to develop the conceptual background of developmental genetics. ….. In retrospect, everybody will certainly agree that it was highly interesting. The focus on Drosophila allowed a continuous flow of material and discoveries of all possible kinds: everything could be done, the tools were available on time, the important questions were asked, and many of them could eventually be answered.

If we leave the quality of our own work outside our considerations, i.e. the work of those who contributed to the development of the conceptual and factual background of developmental genetics, as defined by the Drosophila work, one can conclude that we participated in the development of a major phenomenon in the history of biology. The work with Drosophila was followed eventually by the work with vertebrates, mainly mouse and zebrafish, using, however, the same experimental strategy as exemplified with the fruit fly.

[Precursors and Synthesis] Genetics [as the] science of hereditary transmission attained academic maturity with the work of Thomas H. Morgan and his co-workers [mainly Alfred Sturtevant, Calvin Bridges and Hermann Muller]. Although Morgan was initially an embryologist and a practitioner of the “Entwicklungsphysiologie», [his] work as well as that of his whole school on Drosophila is defined by the strict separation of hereditary and embryological aspects….. Cytology was the first partial discipline to which the «New Genetics», coming out from Morgan’s school, established a connection. Later on, genetics established important connections to biochemistry as well, mainly through the work of Boris Ephrussi and George Beadle with Drosophila and Alfred Kühn with Ephestia. As a follow-up of this later work, most researchers considered gene function to direct metabolic functions.

An important development took place simultaneously, which heavily influenced biological research in general: … the embryological work of Hans Spemann’s school which, in

Fig. 10. José on the *Camino de Santiago* pilgrim’s trail in November 1998. *In the company of Michael Bate, he walked 800 km from Navarra to Galicia (almost the entire width of the Spanish peninsula).*

a manner similar to that in which Morgan excluded embryology, consistently ignored all genetic aspects. However, despite the conscious neglect of genetic aspects of embryology in Spemann's work, and of embryological aspects of heredity in Morgan's work, modern developmental genetics succeeded in integrating both embryology and genetics into the same conceptual frame and was able to use both in its approach to investigate developmental processes.

Several researchers [e.g.(Gilbert, 1985)] believe that the origin of developmental genetics can be defined by .... work on the [mouse] T-locus (Gluecksohn-Schoenheimer, 1938), although ... for sure, [this] origin is much more complex, [perhaps] beginning with Richard Goldschmidt's «Physiologische Theorie der Vererbung» (later translated into English: "Physiological Genetics") (Goldschmidt, 1927, Goldschmidt, 1938), in which the possibility was outlined that genes have developmental functions. Of some importance ... are also the first attempts to correlate transmission genetics with the control of development in Drosophila, represented by Alfred Sturtevant's analysis of gynandromorphs in claret non-disjunction. Considerably more important was the work of Boris Ephrussi and George Beadle transplanting imaginal discs to show that genes control developmental processes. The work with Drosophila was followed by work with other organisms, most particularly by Alfred Kühn and his school, using Ephestia kuehniella, where the relationships between genes, gene function and specific developmental processes could be demonstrated beyond doubt. Work on phage morphogenesis can be considered a forerunner of developmental genetics in higher organisms. The conceptual background used to dissect the self-assembly and morphogenesis of bacterial phages is in fact the same as that ... eventually to be used to dissect development in animals.

The development of developmental genetics culminated in the investigations using Drosophila. The consideration of the work by Christiane Nüsslein-Volhard, Eric Wieschaus and Edward Lewis will therefore occupy a substantial part of the discussion. However, this work did not come out in an empty space. Prior, ... important discoveries had already been made, ... e.g. the techniques for the so-called clonal analysis of development, including the discovery and analysis of epidermal markers, or that of developmental compartments, which related clonal analysis to morphogenesis, and [of course,] the parallel development of the techniques required for cloning and sequencing specific genes..."

At his early death on May 8th, 2004, caused by a myeloma, the manuscript was far from being finished. To his friends, these pieces and fragments, left behind, bring sadness. But the incompleteness - as if still alive - also carries some happy resemblance to José's outpouring arguments and to his multi-facetted, vibrant personality.

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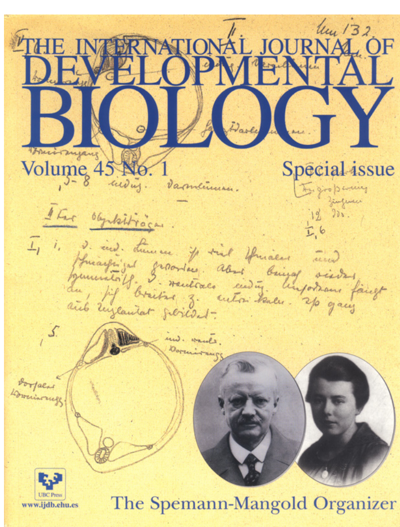

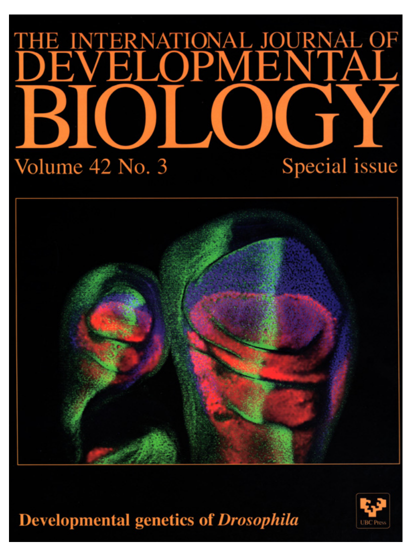

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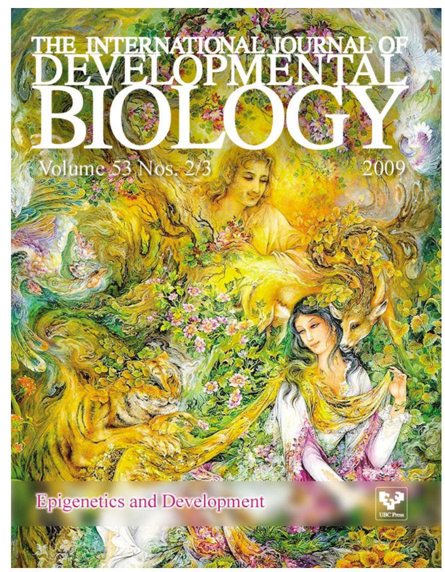

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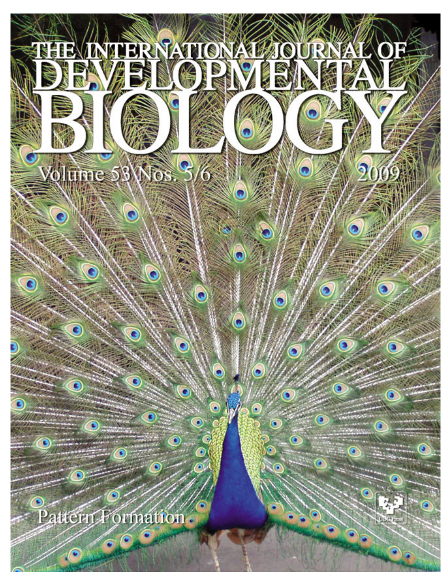

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