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SPECIAL FEATURE

Prescience and critical thought: The life and science of José Campos-Ortega

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José Campos-Ortega was an outstanding scientist and a wonderful human being. In more than three decades of research he made major contributions to studies in both *Drosophila* and zebrafish development. He helped shape our understanding of neural induction and specification in early nervous system development. José was one of the most memorable characters among the pioneers of neurogenetics; full of energy, and a zest for life, he was argumentative in the most positive and useful manner, with a reputation for brutal candour and unimpeachable honesty. He left an indelible impression on the science of every one he interacted with. I am one among the many beneficiaries of his encouragement and concern and his untimely demise in March 2004 leaves a void hard to fill.

The doctor and neuroanatomist

José was born in Spain on 22 August 1940 and graduated as a Licentiate in Medicine and Surgery in June 1965 at the University of Valencia. He was awarded a Doctor of Medicine degree in 1967 after completing a thesis on the pattern of brain stem nuclei in reptiles at the Anatomical Institute of the university. During the initial stages of his career, José focussed largely on the neuroanatomy of the visual system, first on that of vertebrates with Paul Glees at the University of Göttingen and subsequently on flies at the Max-Planck Institute for Biological Cybernetics in Tübingen. Using histological and ultrastructural methods, José described several fibre tracts in the retina and lateral geniculate body in primates, pigs and cats (Campos-Ortega and Glees 1967; Campos-Ortega 1968, 1970; Campos-Ortega and Clüver 1969; Campos-Ortega and Hayhow 1970).

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A list of publications of Jose Campos-Ortega is available as supplementary material on the journal website.

With his move to dipterans, José continued his studies on visual processing though at a different scale, focussing on single cells rather than on populations of neurons. José, together with Nick Strausfeld, explored the synaptic circuitry within the fly lamina and described connectivity, which could provide the substrate for lateral inhibition, which is the basis for contrast enhancement during insect vision (Campos-Ortega and Strausfeld 1973; Strausfeld and Campos-Ortega 1973, 1977).

Deciphering early neurogenesis

In 1973, at an unusually young age for the German academic system, José became Professor at the University of Freiburg where he spent the next nine years. He moved his group to the University of Cologne in 1982, where he remained until his death in 2004. José exploited *Drosophila* genetics and used elegant, sometimes technically difficult but conceptually simple, techniques in an effort to understand neural development in the early embryo. His work helped elucidate the most fundamental concepts of nervous system development. Only a few features of his work will be covered in this article and the reader is referred to a number of excellent reviews written by José for further information (Campos-Ortega 1989, 1991a,b, 1993, 1994a,b,c, 1997, 1998; Campos-Ortega and Knust 1989, 1990; Campos-Ortega and Jan 1991).

Fuchsin staining of embryos carrying small homozygous deletions on the X-chromosome identified genes that specify early steps of neural development. Genes of the *achaete-scute* complex—*achaete*, *scute*, *lethal of scute* and *asense*—are founding members of a family of basic helix–loop–helix (HLH) product proneural genes (figure 1). Loss-of-function mutations in proneural genes result in failure of specification of neural progenitors, leading to a hypoplasic nervous system. Extending the early observations of Donald Poulson, José analysed the hyperplastic phenotype of *Notch* mutations and with his stu-

dents identified several additional neurogenic genes in elegant genetic screens (reviewed in Campos-Ortega 1993).

In the *Drosophila* embryo, neural progenitor cells arise from the ventral neuroectoderm in three waves of differentiation, designated the SI, SII and SIII neuroblasts. The dorsal ectoderm of the embryo forms epidermal cells almost exclusively. What are the factors that contribute to cell commitment in these domains of the embryo? José and his colleagues transplanted marked ectodermal cells either to an equivalent (homotopic) or to a different (heterotopic) region of the embryo (Figure 2). The results allowed the conclusion that cells within the ventral neuroectoderm had the capability to form either epidermoblasts or neuroblasts. Cells from the dorsal ectoderm give rise to epidermal cells, but when transplanted to the ventral neuroectoderm were capable of forming neuroblasts. This suggests that neural fate is suppressed in the dorsal region or that these cells were induced to form neurons in the ventral region.

What is the mechanism that regulates the choice between epidermal and neural fates in the ventral neuroectoderm? At the initiation of specification, a group of cells

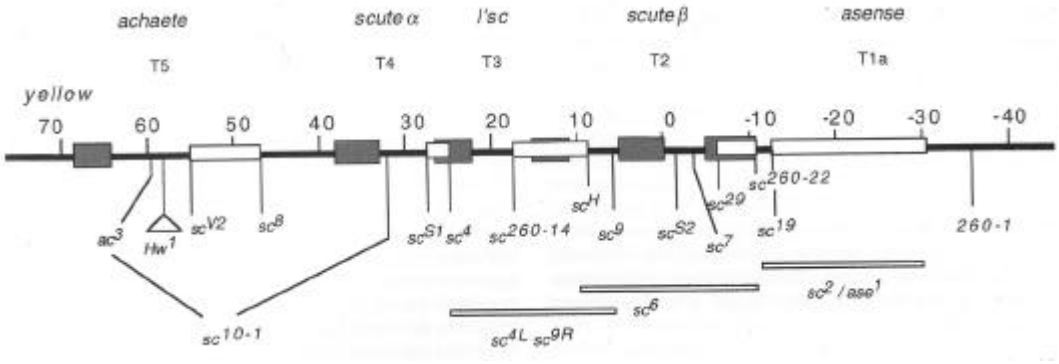

Figure 1. The organisation of the *Achaete-Scute* Complex. The Figure (taken from Campos-Ortega 1998) is based on work from several laboratories but was possible because of the early analysis of the tip of the X-chromosome by José Campos-Ortega and his group.

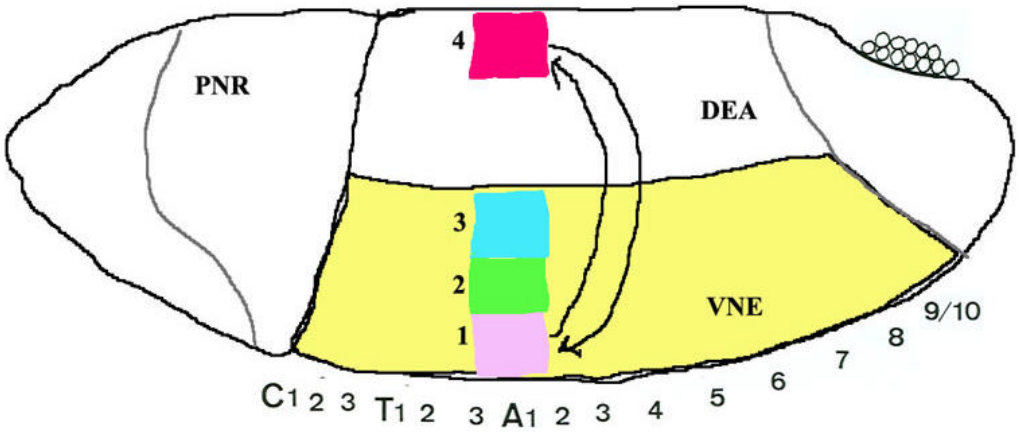

Figure 2. Cell commitment in the neurogenic region of *Drosophila*. Transplantation of marked cells from defined regions of the ventral neuroectoderm (VNE) back to the same position in a host develop as neuroblasts or epidermoblasts. The frequency of neural clones is higher when cells are transplanted from the more ventral regions. Hence region 1 is more neurogenic than 2 or 3. Homotopic transplantation of cells from the Dorsal Epidermal Anlage (DEA) (4 to 4) resulted in epidermal clones.

Heterotopic transplantations demonstrate different properties of the DEA. Ventral cells transplanted dorsally (region 1 to region 4) behave autonomously and give rise to ectodermal as well as neural clones. Dorsal cells, on the other hand, when transplanted to ventral regions (region 4 to region 1) adopt the fate of new location giving rise to epidermal and neural cells. The ability of cells from the epidermal region to adopt neural fates in the VNE suggest either there exist neural suppressing signals in the DEA or could argue for neural inductive cues in the ventral ectoderm.

within the neuroectoderm begin to express helix–loop–helix transcription factors and acquire the competence to become neural (figure 3). One cell from within this equivalence domain is selected as the neural precursor by Notch mediated lateral inhibition. While all cells in the neuroectoderm synthesize both Notch and Delta, one cell, perhaps stochastically, synthesizes higher Delta levels and acts as the signalling cell. Signalling through the Notch receptor results in further downregulation of Delta, thereby enhancing the difference between the two populations of cells. The Notch signalling pathway has been extensively studied in a number of laboratories. During epidermalization, this signalling acts to suppress transcription of the proneural genes and activates expression of the *Enhancer of Split* complex (*E-Spl*). Transcripts of the *E-Spl* complex encode basic HLH transcription factors, which act to specify epidermal lineage. Hence the bias between the neural and epidermal lineage is a delicate balance between the functional activity of two groups of transcriptional regulators—Achaete and Daughterless for the neural fate and the *E-spl* complex for epidermalization.

Return to vertebrates

By the late eighties, there were several examples of conservation of developmental mechanisms between flies and vertebrates. José and his group cloned many of the members of the neurogenic network from zebrafish *Danio rerio* (Bierkamp and Campos-Ortega, 1993; Wülbeck *et al.* 1994; Müller *et al.* 1996; Takke *et al.* 1999; Hans *et al.* 2004) (figure 4). The expression analysis of Delta suggested that transcription is likely to be regulated by the proneural genes. This was confirmed by promoter analysis, which demonstrated that the regulatory regions of Delta in zebrafish and *Drosophila* are likely to be similarly organised. In both cases, the amount of proneural proteins influences the strength of signalling by Delta of Notch. The genes encode helix–loop–helix proteins of the hairy-E(Spl) family and participate in Notch signalling in a manner similar to their *Drosophila* counterparts. While *her1* and *her4* are activated by Notch signalling, *her3* expression is repressed by Notch. Her3 activates its own transcription and also regulates expression of neurogenin, Delta-A, Delta-D and Her4. This provides an additional

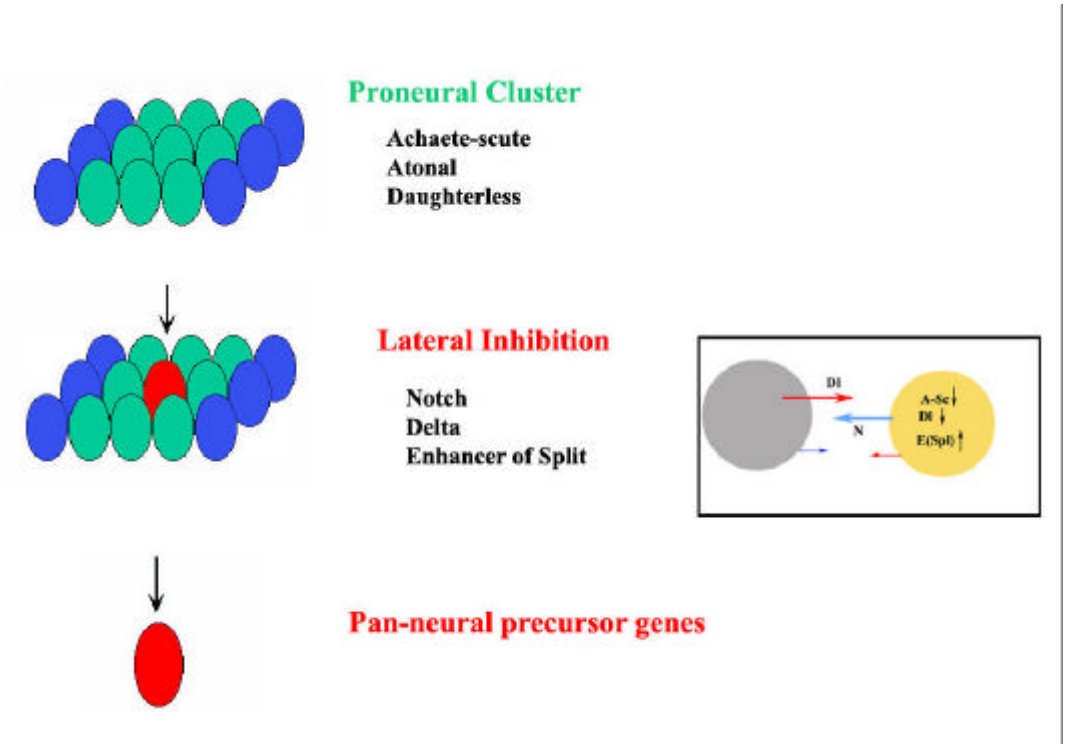

Figure 3. Progressive determination of cells in the ventral neuroectoderm. The expression of proneural genes in a subset of cells in the neuroectoderm defines an equivalence domain where all cells have the potential to become neural. The position of the proneural domain is in turn determined by expression of the prepatterning genes. The neurogenic genes (Notch, Delta) are necessary for singling out one cell that ultimately becomes the neural precursor. This appears to be achieved stochastically since one cell expresses higher Delta which the ligand for the Notch receptor. Activation of the Notch pathway results in downregulation of Delta and upregulation of Notch hence enhancing the difference between the two cells. Notch signaling also turns on Enhancer of Split and downregulates proneural gene expression. This biases the cell towards an epidermal fate.

tier of control of the binary choice of cell fates in the zebrafish.

Jose's contributions are exemplified by his deep understanding of nervous system development and almost a oneness with the system being studied be in flies or fish.

José and India

Apart from being an exemplary scientist, José was also an enthusiastic teacher and played an active role in the dissemination of the excitement of developmental biology to the scientific community as a whole. He taught several courses at Cold Spring Harbor, the Marine Biology Laboratories at Woods Hole and in India and Singapore. Indeed developmental biologists in India, a country very special to him, owe much to José's enthusiastic patronage. His first, of many, scientific visits to India, was to attend the conference on 'Development of *Drosophila*' organized at the Tata Institute of Fundamental Research (TIFR) in 1979 by Obaid Siddiqi and P. Babu. At that meeting and at a workshop held immediately after, José discussed in detail how proneural and neurogenic gene interactions could result in choosing cell fates (Campos-Ortega and Jiménez 1980). All this was soon to become very popular, fashionable and important. But these were the early days of recombinant DNA technology and it required a special ability to appreciate the general and deep value of genetic studies. It was slightly disappointing to José that the audience seemed not to see the sheer elegance of the genetic models being proposed which later became accepted as a general principle in nervous system development.

José returned to TIFR in November–December 1981 when with Nick Strausfeld, he conducted a course on methods in light and electron microscopy (figure 5). It was in this visit that José endeared himself to the community and made lasting friends. He showed by example, that interest in important scientific issues becomes captivating and stimulating. He had a great sense of fun and enjoyed experiencing local cuisine. On one occasion his adventurism prevailed over his wisdom and he was laid low by a Bombay-belly. In bed, he valiantly resisted the

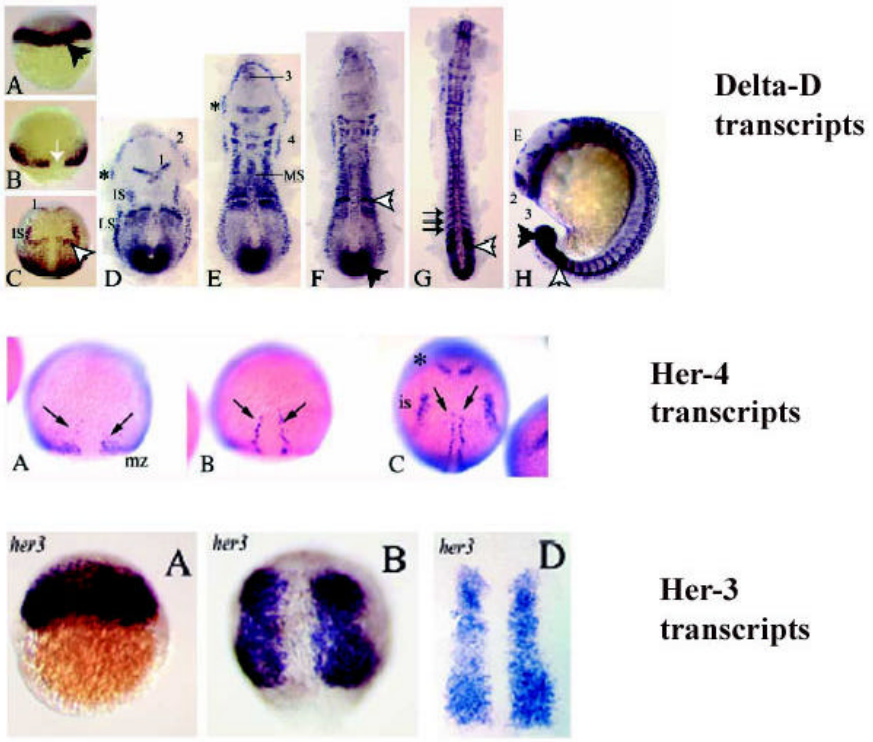

Figure 4. Wholemount *in situ* hybridization showing the expression of different genes involved in neurogenesis in the zebrafish embryo. 1. Delta-D transcripts: (A) 30% epiboly (B) 70% epiboly (C) 95% epiboly. (D) Tailbud stage embryo (E) Two-somite stage embryo. (F) Five-somite stage embryo. (G) 12-somite stage embryo. (H) 20-somite stage embryo. 2. Her-4 transcripts: (A) 70% epiboly (B) 90% epiboly (C) 100% epiboly. 3. Her-3 transcripts: (A) 30% epiboly (B) 70% epiboly (C) section of B showing transcription in the epiblast (from ref. 139). (Modified from Hans S. and Campos Ortega J.A. 2002, *Development* **129**, 4773–4784).

Figure 5. Course on light and Electron Microscopy held at TIFR, Bombay India in November 1980. José Campos-Ortega is in the centre of the first row, Nick Strausfeld is second from left.

efforts of local physicians' attempts to inflict a variety of antibiotics on him. All of us, from students to director, watched with concern at the bed-ridden Spaniard wanting just a glucose-saline drink, jousting with the very puzzled medical profession who wanted to administer some heavy artillery instead. José recovered and returned to Germany with an even stronger affection for India, notwithstanding a few additional bugs in his gut!

Each of his subsequent visits to India was refreshing to old friends and added a new group of students who placed themselves under his tutelage. Many a student having approached him with some trepidation returned pleasantly surprised to find that José took time to listen and offer constructive criticisms of the work being discussed. In 1990, he conducted a course on *Drosophila* neurogenetics together with Michael Bate and Kalpana White and returned in 1992 to attend a meeting held in honour of the founding members of the biology department at TIFR- Obaid Siddiqi and Pabitra Maitra (figure 6). At this time the new centre of TIFR, the National Centre of Biological Sciences in Bangalore was being set up. José was excited to see that research in biology was beginning to grow in the country and he spent many hours animatedly advising his friends. His concern for the well being of his Indian associates was genuine. He was clearly delighted when in 2002, he visited the NCBS in Bangalore to attend the Cell and Developmental Biology symposium, and saw the progress.

This was his last visit to India. José had promised to return frequently and spend extended periods at the TIFR units both in Bombay and in Bangalore. Unfortunately

Figure 6. Conference in TIFR, Mumbai in January 1992. Jose is in the second row third from left; P. K. Maitra is in the first row left next to Kalpana White who taught a course at TIFR in 1990 with José.

this was not to be. With the demise of José Campos-Ortega, we have lost an insightful scientist, a teacher and a friend. His concern, his good wishes and the time he gave to teach and advice will always be appreciated. A whole generation of Indian scientists remember José Campos-Ortega with affection and gratitude.

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