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OBITUARY

José Luis Gómez-Skarmeta (1966-2020)

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'Qué te voy a decir
Si yo acabo de llegar,
Si esto es como el mar,
Quién conoce alguna esquina.
Dejadme nacer que me tengo que inventar.
Para hacerme pez, empecé por las espinas…
Letra: Fito & Fitipaldis "Acabo de Llegar"

What can I tell you?
If I have just arrived,
If this place is like the sea,
Who knows of any corner?
Let me be born, I need to invent myself.
To grow into a fish, I started with the bones…'
Lyrics: Fito & Fitipaldis "Acabo de Llegar"

José Luis Gómez-Skarmeta was a Spanish–Chilean scientist who made key contributions to the understanding of how the regulation of embryonic development is encoded in the genome and how variations in this coding underlie the generation of morphological diversity and genetic disease. A bold, ever-balding scientist, he was tremendously hardworking, generous and supportive (especially of younger colleagues), and always transmitted a contagious enthusiasm. He had a major role in the growth of the Centro Andaluz de Biología del Desarrollo (Andalusian Centre for Developmental Biology; CABD), and also an inordinate fondness for heavy metal music (which he would play in his office or lab at all times), a fondness he softened by hosting a beer hour every Friday for anyone wanting to join.

José Luis was born in Santiago de Chile in 1966 to a Chilean mother and a Spanish father. His years as a child were nomadic, living in Chile, Puerto Rico, Colombia and in various cities within Spain. He studied Chemistry at the Universidad de Murcia, graduating first of his year in Biochemistry and Molecular Biology. After a short stint at Stanford University, José Luis started his PhD at the Centro de Biología Molecular 'Severo Ochoa' (CBMSO) in Madrid.

The early Madrid years

Jose Luis arrived in the laboratory of Juan Modolell at CBMSO in January 1991. The CBMSO was host to some of the most renowned Spanish *Drosophila* developmental geneticists. Within this environment, the Modolell laboratory was pioneering the use in Spain of molecular biology to tackle the analysis of developmental problems, which until then had been pursued mostly by classical genetic approaches. During this period, the lab gathered a plethora of extremely talented students, resulting in the successful characterisation of the proneural genes of the *achaete-scute* gene complex (AS-C) and their roles during the formation of the pattern of sensory organs in the *Drosophila* thorax. To this highly creative environment, José Luis added the trademarks of his personality: energy, directness, comradeship, efficiency, hard work and a killer instinct to identify and solve what he thought were relevant scientific questions. At the time of his arrival, the prevalent hypothesis was that the spatial pattern of bristles in the thorax was the result of the restricted expression of the AS-C genes in clusters of cells in the thorax primordium and that this expression was the result of cis-regulatory elements distributed along the 90 kb of AS-C DNA. Furthermore, it was also proposed that these regulatory elements 'read' positional information conveyed by a pre-pattern of regulators. However, this conceptual framework lacked detail and had yet to be formally demonstrated.

José Luis took on this problem and, in a series of papers that made up his PhD (defended in 1995), provided direct proof that non-coding

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regions of the AS-C could drive reporter expression in proneural clusters, cloned the genes of the Iroquois complex and showed they met all the characteristics expected for AS-C regulators and constituents of the postulated pre-pattern, and identified direct regulators of the Iroquois genes. Together, these papers consolidated a model of pattern formation based on the activation of modular DNA regulatory elements resulting in gene expression patterns associated with ordered cell differentiation. It is revealing that the manuscript describing the cis-regulatory elements of the AS-C ended with the following sentence: 'The regulation of the *achaete-scute* complex thus poses a most interesting case of interactions between promoters and their cis-regulatory sequences.' The two gene families José Luis worked with, the AS-C and the Iroquois complex, shared a number of features: the genes in each family were paralogous, they showed overlapping (but not always identical) expression patterns and they shared non-coding regulatory DNA elements. Understanding the implications of these features and their evolutionary origins set in motion José Luis' research agenda over the years.

To Chile (1997-1999) and back to Madrid (2000-2003)

Soon after obtaining his PhD with Modolell, and in a decade during which *Drosophila* developmental biology was flourishing, José Luis took the bold decision to question whether similar regulatory principles also guide the development of vertebrates. To pursue this question, and seeking a new environment, José Luis decided to give his native Chile a chance. At that time, the developmental biology lab at the University of Chile in Santiago had suffered a serious blow with the death of its leader, Luis Izquierdo. One of his disciples, Roberto Mayor, was advocating rebuilding the group with young scientists trained abroad. The Department of Biology first recruited Mayor, trained in the UK, and he, in turn, convinced José Luis and Miguel Allende to join him to consolidate a group that could bring modern developmental genetics to the country.

With Mayor, who had been working on the *Xenopus* model, José Luis embarked on a project to clone and examine the function of the Iroquois complex genes in vertebrates. Two of the *Drosophila* Iroquois complex genes, *araucan* and *caupolican* (named by José Luis after the Chilean Araucanian indigenous nation and one of its leaders, Caupolicán), had counterparts in *Xenopus* and mouse and, as in the fly, were found to have a role in regulating proneural genes, as well as in defining the neural plate region. During the two and a half years José Luis worked in Santiago, a good deal of his time was spent injecting frog embryos (introducing dozens of constructs into hundreds of embryos each); work he carried out with his wife Elisa de la Calle-Mustienes (his partner in life and essential collaborator throughout his career) and with the students who joined him.

During this time, José Luis started to collaborate with Miguel Allende, which put him into contact with the zebrafish, a model system he first regarded suspiciously but which later caught his attention. After his return to Spain at the end of 1999 – to take up a position back at the CBMSO – José Luis maintained a tight relationship with the Allende lab, including productive reciprocal exchanges of students and postdocs, and continued to work on the Iroquois complex as a paradigm for a conserved cluster of developmental transcription factors.

Around this time, several top Spanish developmental biologists (including Juan Modolell) were members of a scientific advisory board that convened to supervise the launching of a new institute devoted specifically to developmental biology, located at the campus of the Pablo de Olavide University on the outskirts of Sevilla, and synergising with some university departments. This was to become the CABD, and José Luis was among the first principal investigators to be recruited. This was again a bold move: the institute was hardly operational, and a major task for the new PIs would be to get it running. For José Luis, this move had two draws: more space for his planned fish operations and the opportunity to join a number of scientist friends (including Acaimo González-Reyes, Loli Martín-Bermudo, James Hombría and Fernando Casares) in this exciting endeavour. Both motivations were enough for him and Elisa to start afresh at the CABD.

The CABD (2003-2020)

The AS-C and the Iroquois complex genes are just a handful among many developmental genes, some of them also forming clusters, in the genome of any animal. Their controlled deployment in time, space and abundance, depended on regulatory DNA. Deciphering development could not be achieved by just studying *some* developmental regulators; one should look at *all* of them and their regulatory regions. But at the time José Luis was moving his lab to Sevilla, regulatory DNA was hidden within the 95% or so of genomic DNA not coding for (mostly) protein. Furthermore, even if a regulatory sequence was identified, it was often the case that the gene transcript under its control was not easy to determine as these sequences may lie hundreds of kilobases away from the gene promoter they control, potentially with other genes in between. The epiphany, in terms of how to tackle this issue, came to José Luis after learning of work by biologist Thomas Becker and bioinformatician Boris Lenhard who coined the concept of 'genomic regulatory blocks' – regions of high conservation and synteny between vertebrate species that included key regulatory elements as well as transcription units.

Using this framework, José Luis set out to crack the 'regulatory genome' and understand its implications for normal and diseased development and, increasingly over the years, for the evolution of body plans. Foreseeing the potential of zebrafish for his programme, José Luis, together with Fernando Casares, lobbied for a large zebrafish facility, which José Luis got up and running by 2007. This so-called Aquatic Vertebrates Platform became the CABD's flagship and José Luis, as its director, encouraged collaborators to come to the CABD to use the Platform's visitors' lab. Meanwhile, the Gómez-Skarmeta lab was entering at full steam the field of functional genomics. This endeavour was possible thanks to serious investment in bioinformatics, and the recruitment of some terrific young associates, who developed new *in vivo* assays for investigating regulatory DNA function, used chromatin conformation capture protocols for the 3D analysis of chromatin, and introduced epigenomics as a major new focus in the lab. It is important to stress that the take-off of the Gómez-Skarmeta lab would have been more difficult had it not been for Elisa, who was in charge of introducing, implementing and trouble-shooting every new technique before handing them over to students and postdocs. Simultaneously, a collaboration with Jordi Garcia-Fernandez (Universitat de Barcelona, Spain) and two of his PhD students set the Gómez-Skarmeta lab onto an evolutionary genomics track that flourished in recent years and which induced the group to work on a plethora of non-model organisms, including Amphioxus, skate and cave fish to name a few.

This last decade has seen three major whole-genome revolutions: affordable deep sequencing; chromatin conformation capture techniques that provide information on the 3D organisation of the genome; and the genome-wide identification of regulatory regions using biochemical marks (e.g. histone modifications) or chromatin accessibility. The golden age of epigenomics, in which the identification of non-conserved regulatory DNA elements was

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possible, was born. This rising tide led José Luis into the most productive years of his scientific career. Fearless by nature, he and Elisa embraced each new technological challenge with inexhaustible energy through the most difficult years of economic crisis for the scientific community in Spain. Coming from the study of gene clusters, the concept of an underlying genome architecture with partitioned functional domains was very familiar to José Luis. Not surprisingly, investigating the 3D architecture of the Irx cluster in vertebrates was the subject of the first chromosome conformation capture studies in his lab. This knowledge was instrumental to show, in collaboration with the Nobrega lab, that non-coding variants associated with obesity, and physically located within introns of the *FTO* gene, were actually linked to *IRX3*. Moreover, his collaborative work helped to highlight the importance of conserved CTCF insulators as organisers of regulatory landscapes and predictive elements for the assignation of non-coding variants to candidate disease genes in humans.

The emergence of the vertebrate body plan from the ancestral chordate design, and the regulatory logic driving the appearance of morphological novelties, were among José Luis' preferred subjects. To this end, he assembled productive collaborations on a number of evo-devo topics, including the conservation of the active cis-regulatory modules that sustain the vertebrate body plan through the phylotypic period and the regulatory logic driving the evolution of vertebrate appendages in vertebrates, with a particular focus on the fin-to-limb transition. Furthermore, José Luis led a network of international collaborators to establish the amphioxus genome as a paradigm for understanding the chordate-to-vertebrate transition, and revealed that the bipartite architecture of the Hox locus is a vertebrate novelty. Notably, the Amphioxus consortium published the first comprehensive map of epigenetic marks, chromatin accessibility, and transcriptomes across developmental stages and adult tissues of this lovely creature. This constitutes a reference road map for understanding the evolution of the cis-regulatory logic, particularly tackling the effects of the vertebrate-specific whole-genome duplication on gene regulation.

All these studies involved a network of collaborations that José Luis enjoyed personally, with each collaborator becoming a friend for life. As an example, in a good year, José Luis' work would be published in collaboration with 15 different labs – and so many friends. What a joy! The Gómez-Skarmeta lab had become a wonderful place to do science, with an increasing number of students and postdocs, tens of amazing projects running in parallel, and with José Luis supervising – and enjoying – them all until literally his last minutes. This productivity did not go unnoticed: José Luis received a number of recognitions and awards (an ERC Advanced grant, the 'Carmen and Severo Ochoa' Award, one of the highest recognitions to molecular biologists in Spain, both in 2017, and the EMBO membership in 2019).

Parallel to his science, and equally driven by his energy and enthusiasm, José Luis had a major and foundational contribution to the growth of the CABD, an institute he nourished and cared about as one of his major vital enterprises. Together with Fernando Casares and Acaimo González-Reyes, he drew up the first CABD strategic plan, which set the major lines of action that resulted more than a decade later in recognition of the CABD with a Unit of Excellence María de Maeztu award in 2017. José Luis' motto was 'the success of any of us is a success for all'. The influence of José Luis Gómez-Skarmeta will be very long-lasting, and goes well beyond science. His enthusiasm, honesty, brightness, drive, support and generosity have made many of us better scientists and people.