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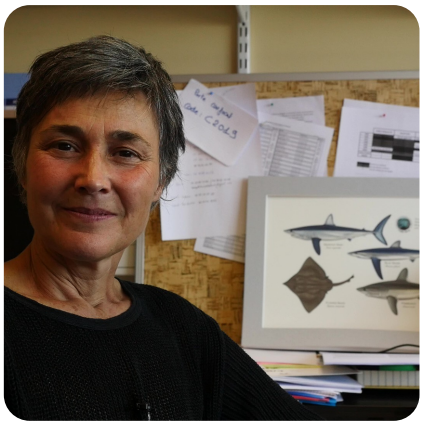
# Meet a *Sci*-Star: Sylvie Mazan



*Sylvie Mazan is a CNRS researcher working in the vertebrate evo-devo field, with a special interest in cyclostomes (agnathans, such as lampreys or hagfishes) and chondrichthyans (or cartilaginous fishes, such as sharks or skates). She is the principal investigator of the "Development and evolution of vertebrates" group at the Observatoire Océanologique in Banyuls-sur-Mer, France. DigitalMarine conducted an interview with her to ask about going into evo-devo, the origin of shark and lamprey models, her research on epithalmic assymetry, and where the next big questions are headed, as well as advice for young scientists.*

**You did your PhD with small nucleolar RNAs; how did you transition to studying development and evolution?**

Yes, I understand my PhD work may seem a priori rather distant from evo-devo! But there was an underlying logic, not readily apparent. In fact, when analysing the structure of small nucleolar RNAs, I was already using comparative tools and approaches. We indeed systematically the test of compensatory base changes in cross-species comparisons to infer secondary or tertiary RNA structures. I had also already addressed the very general question of functional diversification following gene duplication, as much of my work focused on a small family of nucleolar RNAs, encoded by recently duplicated genes in rodents

I was also familiar with "tree thinking" and the first algorithms used to reconstruct them. So, I already had in mind crucial questions on which I later built, albeit using other model systems and other organisms.

I had, for instance, fully integrated during my PhD the idea that comparative approaches are important to decipher the constraints acting on biological systems. I had also become convinced that taking a historical perspective, that is retracing the evolutionary trajectory of a system based on extant states, is crucial to gain a comprehensive view of phenomena. Concerning the choice to switch to developmental biology, it first came to my mind following a seminar which I attended at that time and which was delivered by

Walter Gehring. I then thought that developmental mechanisms had the potential to provide fantastic systems for a comparative, potential to provide fantastic systems for a comparative, evolutionary approach. When I moved as a post-doctoral fellow to the Pasteur Institute to work on a project in developmental genetics, I already had in mind the possibility to later develop an evolutionary perspective of developmental processes. The post-doctoral project in Pasteur gave me the possibility to integrate the concepts and the tools of developmental biology, since I worked on the ES-based inactivation in mice of genes controlling different aspects of head formation. It was an extremely stimulating period, since these systems were completely new to me. But the idea that an evolutionary approach was probably of major interest for these systems was related to projects conducted during my PhD.

**Was your choice to pursue evo-devo at all influenced by a sense that other scientists were going in that direction and that scientists were encouraging you to go, that the future in research was there?**

No, it was really an internal logic. As I got more familiar with developmental processes, I was reinforced in the idea that not only they provided fascinating models to take an evolutionary approach, but also that we had tools to do so, via the study of developmental genes and of their history during evolution. Analyses in an appropriate sampling of species opened the possibility to draw parallels between morphological and molecular evolution, to explore how living shapes -in their fascinating variety- and developmental mechanisms concomitantly diversify during evolution. I was not particularly encouraged by my environment in my choice to pursue evo-devo, either during my PhD, nor during my post-doc in Pasteur but the former gave me the sense of the importance of an evolutionary perspective and the latter the foundations in developmental biology. They thus together contributed to build my conviction that developmental processes provided fascinating systems from an evolutionary perspective.

**Why did you choose shark and lamprey models for your research?**

To make it short, initial impulses came from a scientific question, and then the two crucial criteria that guided the choice of the lamprey and catshark as reference model organisms were (1) phylogenetic position and (2) experimental tractability. Let me develop... During my postdoc in Pasteur, my project focused on a functional analysis of two mouse homeodomain genes, which are paralogues, generated from relatively recent vertebrate-specific whole genome duplications. This of course matched the interest in the diversification of multigene families, which I had developed during my PhD. The project turned out to be even more interesting as the functions inferred from gene inactivation in mice, appeared to radically differ between the two genes, despite their relatively recent common origin.

Furthermore, comparisons across metazoans suggested that some of these functions were very ancient during evolution, while other ones, related for instance to the formation of traits characteristic of jawed vertebrates, had probably been acquired relatively recently, in the vertebrate lineage. When and how had these novel functions emerged, how had they been fixed and partitioned between these two copies? Taking a historical perspective was important to answer such questions, thus addressing in a case study more general ones, such as the part of gene duplication in the emergence of novel functions - including the formation of novel morphological structures.

An obvious strategy, using this multigene family as paradigm, was to explore the timing of the duplication and the molecular modalities of function partitioning between the paralogous

genes. My educational background was in mathematics and physics rather than biology, and to be absolutely frank, I had a rather loose idea of the phylogeny of metaozoans and vertebrates at that time... This is the time when I started to question myself about phylogenetic relationships among vertebrates and to search specimens with appropriate phylogenetic positions within the taxon. Exchanges beyond the community of developmental biologists, with specialists of vertebrate evolution and paleontologists, led me to the conclusion that analyses of cyclostomes (agnathans) and chondrichthyans (cartilaginous fishes), which were until then completely ignored by developmental biologists, were absolutely crucial to address the question I was interested in.

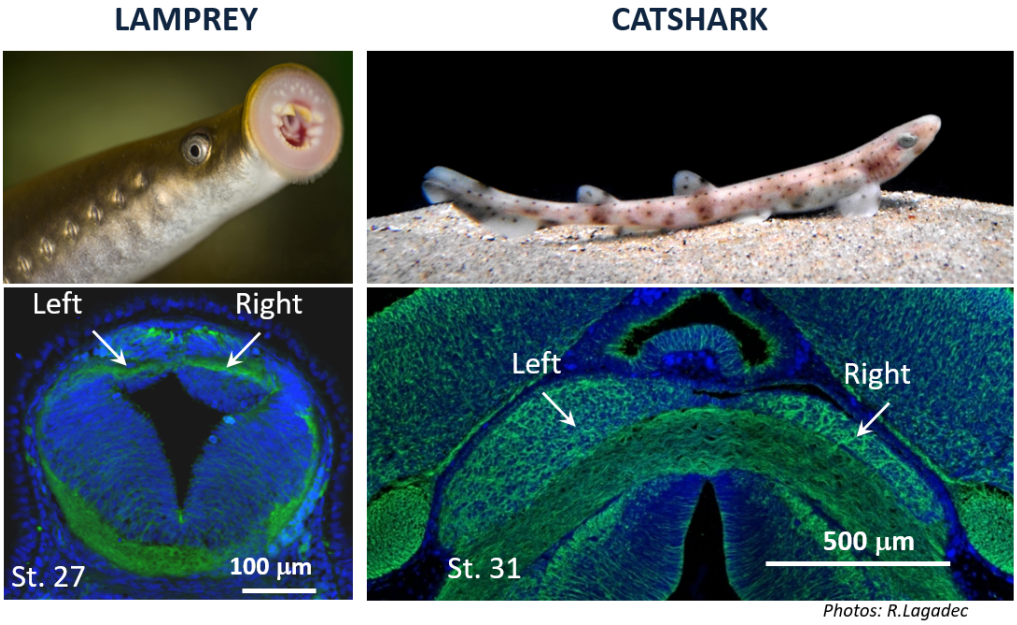
The next step was to reason in terms of feasibility, an access to eggs and embryos obviously being a pre-requisite for developmental biology analyses. The lamprey and catshark then emerged rather logically as model species, because these species are quite abundant and as we realized rather fast, it is not so difficult to produce eggs and embryos. This was the start of a long story! It was a really stimulating, innovative period, with successive limitations being overcome step by step: first egg productions and embryo maintenance in the laboratory, first in situ hybridizations, then first pharmacological treatments and experimental manipulations! We had the enthusiasm of pioneers but in fact, other research groups followed the same logic in California and in Japan: the emergence of lampreys and catsharks as model organisms was starting.

**And when was this happening?**

I started my own research group to develop an evo-devo project in the 1990s, and thinking about it, I was not, at that time, aware of the obstacles we would meet along the way and of the challenges that establishing a new model organism implies -we did not hesitate to invest in the development of two, both lamprey and catshark! In fact, it really took a long time to validate these species as accessible, tractable models for developmental biology. I think that things may go much, much faster today, because of the evolution of sequencing technologies and also because the interest of non-conventional models is now generally acknowledged in the developmental biology community.

**In your opinion, how important is evolution for developmental biologists?**

A developmental biologist is *a priori* primarily interested in understanding developmental mechanisms in an animal in a laboratory environment. An input from evolution is not absolutely required, but I think that this is a very restricted view. First, it does not give any information on how general the mechanisms unraveled are, whether they apply in other species or groups than the one studied. A comparative approach is needed to answer this question. It also says nothing on the mechanisms involved in the emergence of the fascinating diversity of animal forms or on the developmental constraints, which shape morphological changes in complex, changing environments. Finally, I believe that the diversity of living forms can provide a substrate for the discovery of novel mechanisms, even in the absence of the powerful tools generally available in established model organisms, simply because some processes are easier to address in some species than in others. For instance, we are interested in cerebral asymmetries, and more specifically differences between the left and the right in the epithalamus. Such asymmetries do exist in mammals, including humans and mice. But they are extremely subtle and therefore difficult to analyse. In sharks or lampreys, in contrast, there is a huge size difference between the left and the right at the level of the epithalamus. Obviously, it is much easier to analyze the mechanisms of epithalamic asymmetry formation and their biological significance in such species.




Photos: R.Lagadec

*Top: photographs of an adult lamprey head (left, note the round-shaped mouth typical of cyclostomes) and of a catshark juvenile (right). Bottom: histological sections of habenula (epithalamic structures indicated by white arrows) in lamprey (left) and catshark (right) embryos at the stages indicated, showing major size differences between the left and the right. Photo credit: Ronan Lagadec, Observatoire Océanologique, Banyuls-sur-Mer, France.*

## What are you interested in at the moment in research?

We are interested by the molecular and cellular changes that underlie morphological variations. We more specifically focus on morphological traits, whose absence or presence follow recurrent, reiterated patterns during evolution, without a simple phylogenetic logic. Epithalamic asymmetries provide an example of such variations: they are widespread across vertebrates but they considerably vary in nature and degree across the taxon, without a clear phylogenetic logic. Another process we are interested in is the expansion of the egg yolk, which has occurred separately in distant groups of vertebrates - amniotes, elasmobranchs or hagfishes. We are interested in deciphering developmental constraints responsible for the reiterated occurrence of these traits.

At another level of analysis, we are also curious of what the study of non-canonical model organisms can teach us about mechanisms of development. For instance, our model organisms of interest are extremely slow-developing species, harboring large embryos sizes. Until then, such characteristics have been counter-selected in the choice of model organisms in developmental biology, because genetic approaches prevailed. But they reflect a biological reality: could such characteristics imply some developmental mechanistic trends, to be yet elucidated?

## What are the big questions evo-devo scientists are investigating at the moment?

In the last ten years, some major methodological innovations have emerged, which make novel questions accessible in a wide variety of species. This concerns genomics, epigenomics, transcriptomics, with the advent of Next Generation Sequencing, but also imaging with unprecedented temporal and spatial resolutions, and modeling, which allows the implementation of predictive tools for the first time in developmental biology. These tools are not dependent on genetics, they are accessible in a wide range of organisms, and they open new methodological approaches and new conceptual fields, to investigate the molecular and cellular bases for morphological diversification. We are going

through a fantastic period to elucidate the bases for the diversity of living forms...

Our understanding of evolution is impacted by these methodological evolutions beyond evo-devo. Questions of major importance for the future may be: how do organisms interact with their environment, how do they integrate it and adapt to it, in their ecological niche? A revolution is also currently taking place in neurosciences, with the dissection of neuronal and genetic mechanisms regulating behaviors. This again lies beyond evo-devo *stricto sensu*, but this paves the way to the exploration of behavioral evolution.

**Do you have any advice for young researchers contemplating a career in biology?**

My first reaction would be to say that I myself never really followed advice, so that I am somewhat reluctant to give some! To take the question from another angle, I am really happy when I see young scientists deeply interested in an original question, ready to commit themselves to investigate something that they find particularly fascinating.

So the message would rather be an encouragement if needed: stay creative, keep an open mind, follow what you believe in and open new paths -far from career concerns and scientific trends-! This may imply a strong commitment, but those who are ready to take the plunge probably don't need much advice... The questions opened by the multiple, fascinating forms of life, together with novel exploration tools available, offer fantastic opportunities for a curious mind...

From a more practical standpoint, internet offers many ways to identify fields, groups or researchers of interest. Why not contact them to spend some time in the laboratories and take part to the adventure, which science should remain... The scientific community is generally very open-minded and ready to welcome curious people, so go ahead!

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Research group website:
http://biom.obs-banyuls.fr/en/group-5-vertebrates-evolution-and-development-2.html