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DES SCIENCES  
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# *Les traductions des* **Comptes Rendus**

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## **Biologies**

### **Along the road with François**

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Translation posted online: 2024-05-06

<https://doi.org/10.5802/crbio.136-en>


**Abstract:** It was at the Pasteur Institute, in François Gros' laboratory, that I had the opportunity to discover the world of research. An opportunity in more ways than one, first because of the nature of the subject, myogenesis, which lent itself particularly well to cellular and genetic approaches to development and differentiation in vertebrates. An opportunity also because the head of the laboratory, François Gros, who was responsible for the choice of this topic, had created an environment in which researchers could develop their projects with great confidence and freedom.

**Keywords:** Tribute, François Gros, Myogenesis

Original article:

Didier Montarras, "Un bout de chemin avec François". *Comptes Rendus Biologies*, vol. 346, Special Issue S2 (2023), p. 51-53. <https://doi.org/10.5802/crbio.136>

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It was in the summer of 1976 that I first walked through the doors of the Institut Pasteur. I had just been accepted to do a DEA (postgraduate diploma) in general virology. I wanted to know more about retroviruses, especially oncogenic retroviruses; small genome, just enough to replicate, envelope, capsid, polymerase, reverse transcriptase and a powerful oncogenic force that had to reside in an oncogenic gene that wasn't very big. The picture was painted by Marc Girard, our professor of virology at the University of Paris VII. Seduced by the professor's talent and the model, I was convinced. Now I had to find a host laboratory for my DEA. I met Professor Marc Girard, who encouraged me, but his lab wasn't really interested in retroviruses. I also spoke to my high school science teacher, Mrs Jeannette Manigault. She put me in touch with her husband, a former scientist from the Institut Pasteur now working at the university. He suggested a researcher, the husband of one of his students, who had just returned from the United States, where he had been working on avian retroviruses. I met him, we hit it off and we planned to meet again in September. He worked in Villejuif but was planning to move to the Institut Pasteur to join Professor François Gros' laboratory. That's how I ended up working with Dr Marc Fisman in François Gros' laboratory in January 1977.

Marc wanted me to investigate an observation he had made during his postdoctoral work, that infection of cultured myoblasts with Rous sarcoma virus (RSV) inhibits their differentiation. For several years now, Prof. François Gros had been refocusing his Pasteur laboratory on myogenesis, the formation of skeletal muscle in which muscle precursor cells, the myoblasts, stop proliferating and fuse to form muscle fibres, the myotubes, in which a battery of genes specific to muscle tissue are activated. This is a very rich model for studying the regulation of gene expression in vertebrates, which can be approached using cell culture. François Gros' laboratory had several groups working on this topic using mouse and bovine models. Ours was to be a new group, using both an avian model and a retrovirus.

François Gros, who has always been a very busy man, was now director of the Institut Pasteur following the death of Jacques Monod. I was a bit nervous to find myself face to face with him. I don't remember exactly what we said, but I do recall a reassuring exchange. It's a trait of François' personality that I've seen over the years, his ability to analyse and synthesise in an exchange without ever putting the other person in a position of inferiority. Bringing an entire differentiation programme under the control of an oncogene fitted in well with the theme of his laboratory. We didn't discuss oncogenes together too much: we were more concerned with myogenesis and the regulation of muscle gene expression.

The retrovirus of choice for our study was Rous sarcoma virus, which is autonomous for replication and cell transformation and for which thermosensitive transformation mutants (*ts*) had been isolated; transformation is abolished when cells are transferred from 37 °C to 41 °C. So I alternately infected cultured chicken and quail myoblasts with RSV *ts* mutants, to confirm and extend the observation that differentiation is blocked. François summed up the situation well, with a touch of humour, when he said: "So we heat things up and they differentiate".

I showed that the inhibition of differentiation occurs at the transcriptional level and does not seem to be the result of a specific oncogene (*src*, *erb*, *myc*), but rather the consequence of the common activity of these oncogenes to promote proliferation at the expense of differentiation.

I will establish that the blockage of differentiation is at the transcriptional level and does not appear as the fact of a particular oncogene (*src*, *erb*, *myc*) but rather as the consequence of the activity common to these oncogenes to promote proliferation at the expense of differentiation.

After my postgraduate thesis (1979) and then my thèse d'État (1983), my interest in retroviral oncogenes remained, even though my work on myogenesis was more productive in terms of publications. No problem, François encouraged and supported me in my search for a postdoctoral position in a leading laboratory dedicated to retroviral oncogenesis, the laboratory of M. Bishop and H. Varmus in San Francisco. At the end of 1983, I found myself working with M. Bishop to study the presence of proto-oncogenes of the phosphotyrosine kinase family in the genome of *Drosophila*, an organism that should make it possible to approach the function of proto-oncogenes by genetic means. The explosion of molecular cloning and sequencing had shown that retroviral oncogenes originate from cellular genes, proto-oncogenes, captured by retroviral transduction. I discovered another one, but left Bishop's laboratory for family reasons, after two years of screening-cloning-

sequencing, without having done any genetic analysis of this new gene.

On my return to Paris, François welcomed me back into his laboratory where, together with Christian Pinset, we were able to develop a small group. The hypothesis of the existence of a central switch (“master switch”) responsible for the coordinated activation of muscle genes – supported by the work of the laboratories of Helen Blau [1] and Charlie Emerson [2] — was the one that attracted the most attention. The definitive proof of the validity of this hypothesis came with the discovery of MyoD1 (Myogenic Determination Factor 1) in the laboratory of Harold Weintraub [3]. This transcriptional activator was so powerful that its expression could transform a fibroblast cell into a myoblast. Christian’s work on murine muscle cells had established the existence of two phenotypes, one permissive, characterised by the ability of myoblasts to differentiate spontaneously, and the other inducible, where differentiation requires stimulation by IGF (Insulin-like Growth Factor). We were surprised to find that MyoD expression was absent in inducible myoblasts [4]. This must have meant that there was another factor responsible for maintaining the myogenic identity of inducible myoblasts. The answer was not long in coming, with the identification of a second factor in the same family as MyoD, Myf5, by the laboratory of Hans Arnold and Thomas Braun [5]. We were then able to show that Myf5 is indeed present in inducible myoblasts, where it must compensate for the absence of MyoD. Numerous *in vivo* genetic studies carried out by several groups then demonstrated that Myf5 and MyoD are responsible for the acquisition of myogenic identity during embryonic development and are susceptible to complementation. The exchanges with François during this crucial period were stimulating and invaluable. When he left the Institut Pasteur in the mid-1990s, François’ help was once again essential and enabled us to continue our work thanks to the creation of the Cellular Development Laboratory, a five-year group that Christian and I co-directed.

These almost twenty years spent in François’ laboratory gave rise to numerous exchanges, certainly not on a daily basis, but frequent enough to measure how he saw his role as a leader, attentive, close but discreet; in fact, he had created around his researchers, and the whole troupe that makes up a laboratory, a permissive space, a territory of trust where each one could implement their projects. This is a rare quality in a boss of his stature, where dirigisme and authoritarianism are so often the order of the day. As the years went by, the ties between us remained strong, even if our meetings became less frequent. We would meet, usually in the company of Benoît Robert, for lunch near the Académie or the Institut Pasteur. These warm lunches allowed me to get to know François in a different light, where he often adopted the tone of humour that can be found in the chapter *De Pasteur à Monod* in his book *De la Pénicilline à la Génomique, Portraits et Rencontres*. I regret that I have not yet seen the documentary film on Pasteur’s work made in 1947 by Jean Painlevé and Georges Rouquier, in which François, then a young researcher, played the role of Emile Roux.

## 1. Disclosure of interests

The authors do not work, do not advise, do not own shares, do not receive funds from an organization that could benefit from this article, and have not declared any affiliation other than their research organizations.

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