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François Gros' laboratory at the Collège de France

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Abstract: I was recruited by François Gros as a PhD student in his laboratory at the Institut de Biologie Physico-Chimique in 1965, and continued to work with him after I graduated. In 1973, when he was appointed Professor of Cellular Biochemistry at the Collège de France, François decided to set up a team working on neuronal differentiation. He asked me to take part in this new scientific adventure. Here I'd like to talk about the members of his laboratory and some of their scientific work, in particular that on the cytoskeleton of neurons.

Keywords: François Gros, Collège de France, Neurons, Cytoskeleton

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The decree appointing “François Gros as professor of the chair of cellular biochemistry with effect from 15 May 1973” takes us back just over half a century.

For François Gros, this was the beginning of more than twenty years of teaching – a teaching duly renewed each year in accordance with the Collège de France principle, always exciting and well attended – but also, as I would remind you, the starting point of a new episode in his great scientific adventure.

François Gros had already been converted to developmental biology for several years, and had become involved in the field of somatic cell differentiation by launching a major programme to study the genetic regulation of myogenesis in the brand new laboratory that Jacques Monod, who had become director of the Institut Pasteur in 1971, had offered him.

For a while, François thought that the premises he had inherited from his predecessor at the Collège de France, Professor Jean Roche (chair of general and comparative biochemistry), could be used to develop his team working on muscle. However, he soon had the idea that research on neuronal differentiation at the Collège could be a kind of counterpart to the research on muscle differentiation carried out at Pasteur. Yoheved Berwald-Netter, who was already interested in neurogenesis, had expertise in a good culture model, murine neuroblastoma, and was looking for an implantation laboratory. François Gros offered to set up her team in the spacious rooms of his chair at the Collège. With his usual sense of humour, François said that Yoheved’s job was to “wipe the slate clean”. It has to be said that the premises were vast but dilapidated – this was well before the major renovation of the Collège de France orchestrated by Jacques Glowinski – and in fact still largely occupied by former teams from the previous chair. But François also inherited the invaluable help of a very kind and efficient secretary, Sabine Samuel, and an electromechanical workshop with several experienced people who were very useful in introducing new methods into a laboratory. Yoheved Berwald-Nettre quickly set up a functional cell culture room and surrounded herself with her first students, including Annette Koulakoff and Gilles Merlin. She focused on studying the components of the cell membrane as privileged sites of interneuronal and neuromuscular communication.

Shortly after Yoheved Berwald-Netter, François Gros invited several of his students or colleagues from his former teams to join his laboratory at the Collège: Bernard Croizat, Francis Berthelot and Claude Jeantet were the first, followed by Lucienne Legault, Jean Thibault, myself and Marie-Madeleine Portier. Many others joined the laboratory around the research themes that were being established, but unfortunately I can’t mention them all here.

Neurobiology was already present in the laboratories of the Collège de France: neurophysiology with Professor Yves Laporte, neuropharmacology with Jacques Glowinski, neuroendocrinology with Andrée Tixier-Vidal, who worked on the differentiation of anteropituitary and hypothalamic cells in culture, mainly using electron microscopy and immunochemistry. However, it was François Gros who introduced to the Collège the then completely innovative project of studying the terminal differentiation of nerve cells using molecular biology and biochemistry methods. A little later, genetic engineering and monoclonal antibodies would revolutionise all these disciplines and usher in the era of molecular neurobiology.

Initially, the model of established lines derived from a mouse neuroblastoma was very attractive because it avoided the extreme heterogeneity of nervous tissue that makes biochemical approaches difficult. It is possible to obtain a homogeneous mass of neuroblasts, round undifferentiated cells that, after induction using various protocols, stop dividing and express a programme of differentiation towards a neuronal phenotype, such as the emission of neurites – extensions reminiscent of dendrites and axons – and the biosynthesis of enzymes involved in neurotransmitter metabolism or of neuronal cytoskeletal proteins, all of which are “markers” whose evolution and the mechanisms controlling their emergence can be analysed. We can also make global comparisons between the neuroblastoma state and the differentiated state at the level of messenger RNA populations or at the level of proteins. Analyses of specific markers and global approaches have been successfully implemented in the laboratory. However, non-transformed cell models have also been developed, notably by Yoheved Berwald-Netter’s team, who have developed almost pure primary cultures of neuronal or astroglial cells.

I would now like to highlight some important results of the work that was carried out in the teams

that François Gros hosted and supported in his laboratory at the Collège de France. Several concern the cytoskeleton of neurons.

Claude Jeantet's team, which was taken over by Philippe Denoulet after 1981, was interested in alpha and beta tubulins, protein subunits assembled in heterodimers that polymerise in dynamic equilibrium to form small hollow tubes, the microtubules, which are essential for many cellular functions. The development of new high-resolution methods for analysing these proteins has revealed a high degree of heterogeneity in neuronal tubulins, particularly in the central nervous system, which increases during ontogeny. This heterogeneity is the result of both the existence of a multigene family and numerous post-translational modifications [1]. A new and functionally important post-translational modification has been discovered, polyglutamylation [2]. Polyglutamylation involves the sequential addition of a small number of glutamate residues to the C-terminal region of tubulin subunits, greatly increasing the chemical diversity of the heterodimers. This oligomeric modification acts like a molecular potentiometer, modulating the interaction of microtubules with the associated proteins that specify their functions. This modification was subsequently found in other proteins, such as those involved in nucleosome assembly [3], and is catalysed by a whole family of enzymes also discovered in the team, notably through the work of Bernard Eddé.

Collaboration between the teams of Yoheved Berwald-Netter, Philippe Denoulet and Jamel Chelly has shown that doublecortin – whose mutation is responsible for severe malformations of the cerebral cortex in humans – is a protein that associates with microtubules, selectively localises (as shown in particular by Annette Koulakoff) at the ends of neuritic extensions and is involved in the migration of neurons [4].

Marie-Madeleine Portier discovered a new neuronal protein of the intermediate filament family that is expressed mainly in neurons of the peripheral nervous system, but also in neurons of the central nervous system that send their axons outside the latter. It is therefore called peripherin [5]. The functional significance of the extreme diversity of neurofilament proteins still raises many questions. Peripherin appears to be involved in signal transduction between the plasma and nuclear membranes.

Finally, I would also like to remind you that Yoheved Berwald-Netter's team, while working on the ontogenic expression of voltage-gated sodium channels in neurons, essential elements of bioelectrical activity, discovered a new type of channel that is surprisingly present in non-excitable cells, astrocytes. This channel was found to be structurally related to neuronal channels, but differed from them in functionally important regions [6]. In situ hybridisation analyses have shown that this channel is highly expressed in regions of the nervous system involved in hydromineral homeostasis.

It should be remembered that only three years after his election to the Collège de France, François Gros was given the difficult task of running the Institut Pasteur following the death of Jacques Monod. François Gros' capacity for hard work in carrying out his many responsibilities is particularly admirable. In this context, I would like to share with you some personal accounts that show the kind attention that François Gros generously paid to the young people in his laboratory at the Collège. He also took an interest in the work of the marine biology laboratory in Concarneau, which was then attached to his chair and directed locally by Yves Le Gal.

Annette Koulakoff recalls that, despite his busy schedule, François Gros never failed to discuss the progress of their research with the students when he was at the College and also when he met them on Saturdays at the Institut Pasteur. When they returned from their postdocs, they could count on his support for their research projects and his recommendations to help them apply for research positions. He would take the trouble to write detailed letters of recommendation in his beautiful slanted handwriting, which of course carried a great deal of weight.

Jean-Christophe Larcher, a former PhD student in Bernard Croizat's team and then a postdoc in Philippe Denoulet's team, also wrote to me:

"One of the memories I have of my personal relationship with François Gros relates to the almost finished version of my dissertation, which he took the trouble to proofread and correct by hand, asking me only to forgive him for not having had the time to do so for the 'Materials and Methods' chapter! I have carefully preserved this document, which is of particular importance to me."

To this memory, Jean-Christophe adds that long before universities made it compulsory for doctoral students to have a source of income, François Gros would try, and almost always succeed, in finding a grant, a scholarship or temporary work for doctoral or post-doctoral students to bridge the gap between two more permanent sources of funding.

Domingos Henrique, a brilliant Portuguese researcher in developmental biology, was still a PhD student when he arrived in François Gros's laboratory in September 1987 with a one-year grant from the French government. He worked in Philippe Denoulet's team and then, towards the end of his stay, in Yoheved Berwald-Netter's team, where he helped to clone the famous glial sodium channel I mentioned earlier. He wrote to me:

"François Gros was always interested in what I was doing and was kind enough to invite me to lunch on my departure at the restaurant near Pasteur, where he commented on the fine French cuisine! I completed my doctorate in 1991 at the Gulbenkian Institute in the University of Lisbon, where François Gros was scientific advisor. He was one of my examiners. I had to go and see him before my PhD defense at Pasteur to tell him in detail what I had done during my doctorate. He asked me many very stimulating and enlightening questions. It was a wonderful experience to discuss my work with one of the greatest scientists of the twentieth century. I still feel very privileged to have had this opportunity, which also enabled me to meet a fantastic group of scientists and friends who I have kept for the rest of my life."

Another testimony, and not the least important – because it is also a fine example of François Gros' commitment to international scientific relations – was sent to me by Yoheved Berwald-Netter:

"One of the researchers in my team," she says, "was a young graduate of the Ecole Normale Supérieure, Gilles Merlin, who was due to complete his military service, which was compulsory at the time. He was thinking of doing it in a French-speaking African country with which France had a scientific and technical cooperation agreement. I suggested to Gilles that it would be better for his future career to do it at the Weizmann Institute, my 'alma mater', as I like to say. Gilles thought it was a very good idea, but unfortunately the necessary agreements between France and Israel had been interrupted by the Six Day War in 1967. By 1978, the political climate had changed and there was hope that the agreements could be renewed. Michel Revel, a professor at Weizmann, where he was developing a magnificent research programme on interferon, assured us that he would be willing to welcome Gilles if the administrative problem could be resolved, and gave us the contact details of the scientific attaché at the French embassy in Tel Aviv. A long series of steps followed, the success of which owed much to the support and great name of François Gros. The scientific and technical agreements between France and Israel were renewed, and Gilles was the first coopérant to benefit from them! He stayed in Michel Revel's laboratory for three years, and when he returned to France, he was able to continue the work he had started there and apply for a position at the CNRS, of course with the support of François Gros."

The legendary kindness of François Gros was illustrated in another way when it came to a researcher from his laboratory at the Collège de France, Francis Berthelot. While actively working in Bernard Croizat's team, Berthelot had begun to publish science fiction novels (some of which won prizes), and towards the end of the 1980s he wanted to move to a human sciences section of the CNRS. François Gros respected this personal evolution and helped him to make the change.

François Gros was not only benevolent, but also devoid of the slightest trace of authoritarianism, an exceptional quality in such a great researcher.

All those who had the good fortune to do research in his wake owe him a huge debt of gratitude for the freedom he gave to teams and individuals, without ever failing to provide his invaluable advice and support.

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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