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A tribute to François Gros, a founding father of molecular biology

Our journey with François Gros

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Abstract. Gillian Butler-Browne began working on muscle at the Institut Pasteur in the laboratory of François Gros in 1978. She characterized the expression profile of different myosin isoforms during both human and rodent development. Vincent Mouly joined this laboratory for his PhD in 1982, and defined the different populations of myoblasts appearing during development in birds and then in humans. Together, they demonstrated the impact of the limit in proliferation of the precursor cells on the regenerative capacity of human skeletal muscle, and their group developed models to evaluate the regenerative potential of skeletal muscle *in vitro*, measuring the telomeric erosion, and identified the involvement of a stress pathway in the proliferative arrest of muscle progenitors. A platform to produce human immortalized muscle cell lines was the successful result of this research, initiated with François Gros and W. E. Wright. The *in vivo* regenerative potential of human muscle cells was evaluated by injection into muscles of immunodeficient mice. Their group in collaboration with the clinical team of Professor Jean Lacau St-Guilly and Professor Sophie Perié completed a successful autologous myoblast transplantation clinical trial for Oculo-pharyngeal muscular dystrophy. This common scientific career was made possible thanks to the precious and always benevolent support of François Gros.

Keywords. Actin and myosin isoforms, Classes of myoblasts, Immortalization, Muscular dystrophies.

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Gillian Butler-Browne

I carried out my PhD as a travelling SRC/UK scholar studying the reconstitution of chromatin using various biophysical techniques. I was working with Dr. Stanley Bram at the Institut Pasteur to carry out X-ray diffraction on chromatin extracted from calf thymus. This entailed weekly visits to the local “abat-toir” (slaughterhouse). At the same time François Gros lab had chosen to isolate myoblasts from calf fetuses in order to make large-scale cultures to isolate RNA, and this is how I met the people from François Gros’ laboratory at the Institut Pasteur who instilled in me my interest for muscle biology.

François Gros then allowed me to learn the technique of culturing muscle cells while I was still finishing my PhD, and to join into the lab reunions in his office. In 1977, I was awarded a fellowship from the Royal Society in London to undertake a postdoctoral fellowship in François’ laboratory with the aim of studying with Bob Whalen the expression of isoforms of contractile proteins specific to the differentiated state. We used, or developed, several biochemical techniques to characterize the contractile proteins expressed during myogenic differentiation in primary rat and calf cultures, as well as in cell lines such as L6 [1]. The Institut Pasteur was a very nice place to work, bubbling with activity, great seminars and good discussions, François’ door was always open to discuss experiments, and he even came and pipetted sometimes next to us in the lab while we showed him our latest techniques and results.

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Using the 2D-electrophoresis we had developed in the lab, we identified three different isoforms of actin, two present in myoblasts and one specific for the differentiated myotubes. We also identified a new myosin light chain (MLC1emb) characteristic of embryonic muscles and cultured cells [2]. At this time, I also had my first child who spent many evenings sleeping in François' office while I set up my experiments. By using a combination of novel techniques developed in the laboratory, including peptide mapping and native gel electrophoresis, we also identified two new myosin heavy chains isoforms, embryonic and fetal/neonatal that were specific to early stages of muscle development and differentiated myotubes in culture [3]. The work I carried out in François' laboratory at the Institut Pasteur led me to define certain stages of embryonic skeletal muscle development in molecular terms, using rodents as a working model and myosin heavy chain as the main marker. I was thus able to define the order of expression of the different myosin heavy chain isoforms during development and their regulation by the nerve and by hormones [4]. François always gave us the freedom to follow our scientific projects as we felt best, the money always seemed to be available to carry out our projects, if not he pushed us in the right direction to look for financial support. We were also encouraged to present our data at international meetings, which was quite hard when you were presenting data which went against the dogma in the field. François had asked me to present my data at a Gordon conference and at a FASEB meeting, a great start to a career. The notion of developmental isoforms was not easy to get accepted, especially when you present this as a young postdoc at this sort of international meetings. It was during my postdoc that I also met some of the people that were to become very important to me. Ketty Schwartz, director of an INSERM Unité working on the heart, who will later become head of the research unit of the Myology Institute, came to work with us in the lab to learn the different techniques we had developed and apply it to the heart. She was a great scientist and friend and helped me many times during my career. François also introduced me to Michel Fardeau, a clinician internationally renowned in the field of neuromuscular disorders and future head of the Myology Institute in Paris, AFM (French association against myopathies) and particularly Bernard Barateau, who was then president of AFM. The dis-

cussions between us directed the rest of my scientific career. It was thanks to these discussions with François, Michel and Bernard that I applied all the knowledge and technology I had developed to study human muscle development and disease. It was also thanks to a lunch with Professor Mongi Ben Hamida, a distinguished clinician then Minister of Health of Tunisia, that I discovered Tunisia and the Neurology Institute where I made many trips, setting up the novel techniques of immunohistochemistry in his service. Some of the best muscle biologists seemed to have passed through François' lab and this gave us an amazing place to work.

Vincent Mouly

I joined the laboratory of François Gros, the famous 6th floor of the Monod Building in Pasteur, in 1982. My past education was not particularly brilliant: after failing medicine (I made substantial progress on saxophone at that time), I had enrolled in biology in Jussieu. I had spent 18 months in Pasteur Dakar in Senegal (as a surrogate to military services) and was looking for a lab to host me for my DEA (which was the equivalent of master 2 at that time). I visited several labs in virology (my field at that time) in Pasteur, including that of Marc Girard, and added at the last minute the 6th floor advised by Denise Paulin, who headed the DEA of microbiology. I first met Marc Fiszman, who was heading a team in François' laboratory, and still keep a vivid memory of my first steps on the 6th floor. Marc had a tiny office open on a tiny lab of two small rooms, packed with people. Marc was extremely nice, smoking his pipe and listening to FIP (the French jazz radio station), and my decision was immediately taken. There was still a pending problem: Marc was working on muscle cells in birds, with very little connection to virology! This was the time of the boost of oncogenes, and Marc had shown in a *Nature* paper in 1975 that temperature-sensitive expression of sarc, the oncogene of the RSV, could allow manipulation of muscle cell differentiation. There was the link! I joined the 6th floor to work with Marc and Didier Montarras, who was finishing his these d'État (much longer than the PhD) with Marc and taught me everything about oncogenes. I met soon after François, whose office was at the other end of the corridor, guarded by Geneviève Antolini and Annie Lassudrie-Duchêne. François had

just resigned from the direction of the Institut Pasteur to work as a scientific adviser to the prime minister. Needless to say, exchanges with him were as precious as sparse, and usually late in the day (or early in the night). I was very impressed, but surprisingly, I discovered an extremely humble human being who was eager to see what results I could get in the field of muscle development (I was not completely convinced that I would get anything worth it at that time...).

Even though the presence of François on the 6th floor was unpredictable, his spirit was always present, and there was a familial atmosphere in the lab. Most of the people working there did not count the amount of time they spent in the lab. This scientific community was extremely rich for a young student like me, with the group of Margaret Buckingham at the other end of the floor, that of Bob Whalen and Gillian Butler-Browne next to us, and the smaller groups of Michel Crépin and of Josette Rouvière-Yaniv. Different families coexisted on the 6th floor: Danièle, the wonderful wife of François, was working in our group, Catherine (also from our group) and Adrian Minty from Margaret's, Gillian Butler-Browne and Bob Whalen, Arlette Cohen, another wonderful woman, who was François' niece and worked with Margaret, to quote some examples. I quickly learned that the 6th floor was now my house, as it was for many others, and that François was the godfather and the guardian angel of this wonderful group of people. I realize now the incredible luck I had to cross François' path: most of the people I worked with in the next years, I met them while they were visiting François' lab, which was one of the main centers for research on muscle worldwide! And I had also the opportunity to be sent to international meetings where I could easily realize that my "scientific family" was a leader in the muscle field! Margaret and Bob were often keynote speakers, and always fighting with all the biggest labs working on muscle worldwide. This is how I met leading scientists in the muscle field, such as Helen Blau from Stanford University, Woody Wright from the University of Texas, South Western (who was to become a close friend), Bernardo Nadal-Ginard, a cardiologist from the Children's Hospital in Boston, or Hans-Henning Arnold from Hamburg, and so many others. These, along with Margaret, were pioneers in the newly emerging field of myogenic transcription factors. Belong-

ing to François' lab was the true valid passport to be accepted in that community, and to be invited to the beer sessions where the people I considered as world leaders were exchanging information! Of course, there was some pressure since the average scientific level on the 6th floor was very high, but that pressure never came from François, who was always encouraging and finding interests in every single piece of scientific information that was brought to him. As an example of that pressure, I still remember participating to what was presented to me as an informal meeting in Concarneau, where François asked me to present my PhD project (you did not say no to François). I realized that this was a common lab meeting between the 6th floor and the lab of Sydney Brenner, who was to become soon Nobel Prize. I also made my first oral short communication in Keystone at midnight, while still a young PhD student, presented by Steve Hauschka, from the University of Washington in Seattle, who pioneered the field of myoblasts during development which was the topic of my PhD [5]! Seminars were also impressive at the bottom of the Monod building, which also housed at that time François Jacob and Jean-Pierre Changeux (who later moved to the new Biotechnology building). Nicole le Douarin, who was heading the Institute of Development in Nogent, was visiting sometimes, and I was sent to her lab to bring my "expertise" (I certainly did not think I was an expert in anything at that time) in 2D-gels and western blots (they call that proteomics nowadays), which I used to study tropomyosin isoforms [6–8]. One day, a young (but older than me) Italian scientist visited Marc, and I had to explain to him what I was doing while he was waiting for Marc. I was petrified to realize that this was Giulio Cossu, from La Sapienza University in Roma, another main actor in the field of classes of myoblasts during development and one of our strongest competitors with Franck Stockdale, from Stanford University (whom I also met in Keystone). The people who had joined the 6th floor before me, or did after, also became close friends at that time (I remember Marc's next student after me, Domenico Libri, who later on played a major role in the RNA biology field, David Sassoon as a postdoc in Margaret's, and Gary Lyons, another postdoc who became a very close friend, and so many others), and we also had discussions with François' other lab in Collège de France.

The second difficulty after convincing the University that my PhD contained some elements of virology, was to find a date for the defense of my PhD! I wanted to have Nicole le Douarin as part of the jury and finding a common slot between Nicole and François took over a year (but that was worth it, and I offered Nicole a piece of cake (a somite) especially made by a friend and representing a chick embryo!) I will never thank enough François and Marc for allowing me to meet all these impressive scientists and to be able to join such a community.

Some changes in my personal life confirmed that François was really a gentleman. I had met Gillian Butler-Browne and we became partners in science and in life. Needless to say, this introduced some perturbations in the 6th floor atmosphere, but François (and Marc) was always supportive in these hard times, as he has always been since. The next step was what to do next. My personal situation was complicated (I already had two boys, and Gillian had two girls), and Marc offered me to stay after my PhD to work part-time on his projects and to develop mine during the rest of the time, with the blessing of François. I realize that if I got a position at CNRS in such a configuration, this was certainly due to the constant support of François and of Nicole le Douarin.

Our common path with François' support

We had developed interest for human muscle pathology, and François was then the head of the scientific board of AFM (the French muscular dystrophy association). He was deeply involved in this new role (on top of the numerous ones he was playing in French and international science) and introduced us into the AFM circle which we never left since. AFM had already supported the last year of my PhD, and we decided to engage into research on human muscle and dystrophies. Through François, Gillian had already met Michel Fardeau, deeply engaged into this field, and François encouraged us to go in that direction. I joined Gillian in her new location at the medical school in rue des Saints-Pères, where we started a small group on human muscle development and pathologies. This is when Woody Wright came back into the picture by encouraging us to work on telomeres in human skeletal muscle stem cells. Woody had been a brilliant postdoc in François' lab, before coming back to the aging field and creating

his own lab in Dallas (he made his PhD with Leonard Hayflick, a pioneer in the aging field). François never forgot us, and always supported us after our departure from the 6th floor. I remember he invited us to a meeting in the Mérieux property, and, as he often did, asking me at the last minute to present the telomere subject. I thought I had a good excuse: no slides (this was the time when slides were real slides, not PowerPoint). No problem, François told me, you will use filter pen and transparencies! Again, you don't say no to François, even though Jim Watson was there. He also introduced us into the field of stem cells through dedicated meetings and networks at the Académie des sciences (we even wrote a paper together on this topic [9]), where we met many collaborators with whom we set up the INSERM stem cell network (including Thierry Jaffredo whom I had met when he was in Nogent, Marina Cavazzana from Necker who was a pioneer in the field of cell therapy for blood diseases, Georges Uzan from Paul Brousse Hospital, Laure Coulombel from Gustave Roussy Hospital who initiated the *médecine/sciences* journal, and many others). I now realize that I started working on cellular senescence and immortalization when I started my PhD in François' lab, although Woody and I managed to publish overcoming of senescence in myoblasts only in 2007 [10] (a project we started when I visited him in Dallas in 1998). François was never very far from us, we visited him every now and then (not often enough) at the Académie, and he offered us to join a research unit in Pitié-Salpêtrière in 1998, a lab directed by Marie-Madeleine Portier, one of François' collaborator in Collège de France. She was retiring, and François thought Gillian could take over. Once again, François was offering us an opportunity to move forward in our career, and to set up our own lab next to the Myology Institute founded by Michel Fardeau and Ketty Schwartz, and where Marc Fiszman had moved. This represented an important step in our scientific journey, since we now could dedicate all our efforts to human muscle pathologies and regeneration, with the constant support of AFM. We then joined the Myology Institute when Thomas Voigt took the head, and Gillian joined the scientific secretary of AFM while I joined the scientific board of AFM. François was still deeply involved in AFM and Téléthon, and I am convinced that he was involved in the invitation we had with AFM by the President at Elysée. Gillian Butler-Browne retired in August 2018 from being director of the newly created Centre

of Research in Myology situated within the Myology Institute in the GH Pitié-Salpêtrière. François came as an old friend to the meeting we organized for Gillian's retirement, when so many of the friends we had met through him came. Gillian is now an emeritus scientific director, while Vincent Mouly is still co-heading their group with Capucine Trollet, and is also involved in managing research bodies at Sorbonne University.

During all these years, from the family of the 6th floor to that of AFM and to the Institute of Myology, François always supported us with kindness. He opened many doors for us, and without him, we strongly doubt we could have even imagined what would be our scientific career. He was a fascinating human being, who combined extreme intelligence with human understanding of what other people could do. We consider meeting him was the best thing that ever happened in our life, both scientifically and personally. We learned so many lessons from him, including working hard, but also scientific and human integrity. He was a true scientific gentleman who pushed the limits of knowledge, imagination, and scientific honesty to an extent that few people have reached. Within his brilliant career, he helped so many people that it is hard to understand how he found time to still push these limits. And he did that with a humility that only extremely talented people can afford. Thank you François for all your help and support, for all the wonderful time we had with you, but mainly for being such an example to the following generations.

Declaration of interests

The authors do not work for, advise, own shares in, or receive funds from any organization that could

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