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François Jacob, or the thirst for novelty

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Abstract

François Jacob tackled embryonic development from 1972 onwards, in the "Génétique cellulaire" Unit of the Molecular Biology Department at the Pasteur Institute, taking as models teratocarcinoma and the early stages of mouse embryo development. Studies on teratocarcinoma provided no major information about developmental processes, but they were the essential step without which embryonic stem cells (ES, iPS) would probably not have been discovered. The mechanisms of development were revealed by genetic approaches coupled to molecular biology, but with the Drosophila model rather than the mouse embryo. Since these studies, it has been revealed that developmental mechanisms among animals have proven to be universal. None of these results were predicted in 1972.

Keywords: Teratocarcinoma; Embryonal carcinoma cells; Embryonic stem cells; iPS; LacZ; miRNA

La science est imprévisible … Il est vain d'espérer prévoir la direction que peut emprunter une science … La recherche est un processus sans fin dont on ne peut jamais dire comment il évoluera. François Jacob [3].

1. 1972: tackling embryonic development

François Jacob accepted me as a thesis student in his laboratory in September 1972. He had in mind a theory concerning embryonic development that he had been developing since the end of the 60s. The choice of his new experimental model, which combined teratocarcinoma, the T/t complex (a series of mouse embryonic lethal mutants) and the early mouse embryo, along with the organisation of his laboratory that he had just finished setting up, reflected the undertaking of an extremely ambitious plan to test his theory.

I only have partial memories of my first interview with François Jacob in July 1972, at the end of my DEA in in-depth Genetics. I arrived, my pipe in my mouth, sent by Gérard Buttin, oblivious to many things. I did not completely realise the extent to which the education in genetics and biochemistry that I had received at the University was exceptional, being delivered either by some of the greatest direct actors in these disciplines or by their best colleagues. François Gros, Gérard Buttin, Raymond Dedonder, Michel Goldberg, Piotr Slonimsky and Madeleine Gans were all part of the finest. I did not understand either the sum of the qualities and circumstances needed to manage to pierce a secret of life. Furthermore, I did not know that I was going to approach this problem, because the thought out attempt that was to be presented to me at the interview, to attack one of these secrets, namely embryonic development, driven by one of the greatest biologists of the 20th century, would fail concerning this point.

Upon my arrival, the Professor took my CV from the hands of Gisèle Houzet, the secretary, cast a rapid glance over it, and exclaimed with a malicious smile "you only got a grade B in structural biochemistry?". It should be understood that he noticed the rest of my CV that was much better; in fact nothing escaped his eagle eye, but in the end the CV was not of great importance. I had just been submitted to the extremely succinct manner that François Jacob had to transmit several messages simultaneously, in a short sentence that contained at the same time the postulates, demonstration and conclusion for

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two or three subjects. This type of condensed communication, where anything in excess was excluded, was his natural manner.

He then bade me enter his office and seeing my pipe, his first gestures were to offer me some tobacco and to fill his own pipe. The interview, which was extremely relaxed, took place in a thick cloud of smoke and François Jacob was extremely seducing. He explained my future role to me: I would work on cultured teratocarcinoma cells with Hedwig Jakob, isolating new cell lines and studying what was then known as cell determination. At that time, thesis programs were thus elaborated by several oral exchanges in the absence of any administrative constraint! I remember that at the end of the interview, I asked him for a few days of time to think things over before committing myself to begin work in the September. With hindsight, this seems to me extremely inappropriate and strange. I never found out whether he was irritated, intrigued or amused by my request.

The atmosphere was installed. It was obvious that one had to pick up and understand things that were only sketched out and react quickly.

Other than Hedwig Jakob's cell culture group (which included Thierry Boon), three other groups were established, each with a specific aim. Hubert Condamine and Charles Babinet's mouse embryo group had the task of supplying normal and T/t complex mutated embryos at the early stages of development. The immunology group of Karen Artzt, Philippe Dubois, Gabriel Gachelin and Marie-Hélène Buc, was responsible for analysing by immunological and biochemical pathways the central premise of the theory, the teratocarcinoma cell membrane. Hence, the understanding of "developmental logic" should arise. Jean-Louis Guénet's mouse genetic group (with Jean Gaillard and Robert Fauve) was in charge of supplying the mice for tumour transplantation, embryos and genetics. These groups should act in a concerted and organised manner, like battalions directed against an objective. In François Jacob references to military organisation were more than implicit, to him research was a battle to be won. He was the general and we were the troops. By the end of 1972, the battlefield and the troops were in place and François Jacob was extremely impatient to give the order to attack.

2. What's new?

During the period that followed, certain subjects and people were extremely closely supervised and even almost controlled. However, this directive manner of working was only one of two ways that François Jacob interacted with his collaborators. The other was almost the opposite, some people having total intellectual and experimental freedom. In the mind of François Jacob, these people were the reserve troops, but he expected that they would generate new data and concepts. Effectively, François Jacob liked nothing better than to be astonished by an idea, a result or an experiment that he hadn't thought of. Moreover, he had somehow institutionalised this way of working by an injunction of "what's new?" that he threw out when he left his office and passed someone in the corridor. Obviously, this "what's new?" did not apply to anything that had already been defined. Furthermore, this "what's new?" placed the verbal exchange straight away at the level he wished it: as high as possible. It was a goad to surpass oneself, but also a permanent pressure.

He sifted through the list of "new fodder" that we presented him with, without pity, punctuating the discussion with "and what else?". Thus, we passed on without tarrying to the following new thought without stopping to discuss the "previous new" that we had just presented, which was no longer new or interesting. The absence of comments concerning the new, in his eyes "old hat", was an order not to waste our and his time with low calibre experiments or ideas. In contrast, when he detected something that tickled his interest, a passionate discussion ensued on the subject and its potential implications. In the best cases he gave out encouragements. Then he came back again and again. The exhortation to persevere was a measure of his lack of interest in subjects of low grade, without risk or ambition.

At the beginning of my thesis, when with Hedwig Jakob I was aiming to isolate new teratocarcinoma cell lines, Boris Ephrussi (one of the giants who, among others outstanding achievements, brought teratocarcinomas to the limelight) gave us the F9 cell line. As this gift did not display all the expected properties, we looked for alternatives and I had the idea that it should perhaps be possible to isolate these cell lines directly from mouse embryo genital ridges. With the help of Karen Artzt and the mouse embryo group, we set-up an experiment where Karen taught me how to dissect genital ridges from embryos prepared by the embryo group. As soon as I presented my first (unfortunately negative) results to François Jacob in response to one of his "what's new?" questions, he was immediately interested, and to conclude he told me "Jean-François, when you have something new in the laboratory I want you to show me it". Furthermore, he told me not to hesitate to disturb him when we had our next dissection of genital ridges planned.

He also spent long hours with myself and Hedwig Jakob in raptures, discussing in front of cell culture plates where from stem cells, contractile heart cells, muscle cells, pigmented neuroepithelium and clusters of nervous cells appeared as if by magic (Figs. 1 and 2) [8].

Many years later, in 1984, he showed the same enthusiasm when I showed him extremely preliminary experiments that I had carried out with John Rubenstein showing an effect of anti-sense RNA. Then, he returned regularly looking for news and even a long time after John had left the lab he insisted on the importance of this subject and pushed me to continue the study (even though we failed to generalise the observation). His attachment to «our» idea derived doubtlessly from the fact that it took up (without us realising it!), François Jacob's first hypothesis concerning the lactose operon repressor. He initially imagined this to be an RNA molecule, before he discovered that it was a protein. This illustrates perfectly François Jacob's incomparable ability to virtually instinctively identify good ideas, to not abandon them and to re-use them