

Supporting information (Mixed feelings about the Nobel prize 2011)

S1: Organograms of the Hoffmann laboratory in 1992-1995- (see FigS1) (minor errors are possible).

Like traditional French laboratories, the Hoffmann lab was organised into sub-teams. This series of organograms clearly shows that the work on Toll (and more globally genetic studies indicated by a red *) was not the laboratory's priority during 1992-1995. None of the lab's key technicians, nor its "best" PhD students, were injected into the Toll project at that time. For instance in September 1993, none of the 7 students starting their PhDs or DEA (masters) began work on a genetics-based project, at a time when I was already working on Toll!

Things improved later¹ but this was mostly due to the personal initiatives of individual researchers rather than any suggestions from the lab managers. Indeed, the technicians probably had a better perception of what was really going on in the laboratory than either of my lab chiefs. An analysis of the laboratory's publications during this period (1992-1996) shows that the most productive work was performed by Philippe Bulet's team, working on antimicrobial peptides, and myself. Blue * indicated persons involved in the characterization of the κ B binding site or the κ B binding protein.

¹: In September 1994, Emmanuelle Nicolas started her PhD with me on *cactus* regulation after a DEA (masters) degree with Philippe Georgel (in JM Reichardt's team). This was her decision to join me since she was interested by the genetic approach. I also benefited from a 1 year 50% post-doc, Elizabeth Kromer-Metzger, who helped on the Imd project but was rather inexperienced in genetics. A cleaning lady, Raymonde Syllas, also started to work with me half time, taking care of the fly stocks and fly food production.

S2: Analysis of the respective contribution to the 1996 Cell paper:

Bruno Lemaitre: ordered the Toll pathway mutant lines, designed all the experiments, organize the work with other people, analyzed all the experiments, wrote the paper.

Emmanuelle Nicolas (PhD student who worked under my supervision): helped me in a number of key experiments and did a polyA RNA Northern blot that showed many Toll pathway genes were induced upon infection (requested by a reviewer = Figure 7).

Lydia Michaut (PhD student of Marie Lagueux): probed few Northern blots with the Drosomycin probe, including the first one that showed constitutive activation of Drosomycin in Tl^{10b}. Lydia had cloned the Drosomycin cDNA (published in Felhbaum et al., 1994) and I found it fair to associate her with my project since her own had not worked out so well.

Jean-Marc Reichhart: he initiated the work on Dorsal but showed little interest in my research during the two years that followed. In fact, from my point of view, his major contribution was limited to occasionally allowing, Reine Klock, one of his many technicians to work for me and extract RNA from whole flies to perform Northern-blots.

Jules Hoffmann: Helped write the final version of the paper and discussed the results.

Other contributors:

René Lanot did the EM scan of a fungi-infected fly that I gave him (= the cover photo on that issue of Cell).

Reine Klock (technician): extracted total RNA and ran gels of most Northern blot, (I did all the other steps of the Northern blot that included successive hybridization with 6 probes).

Raymonde Syllas (technician): flipped my fly collection and made the fly medium.

Marie Meister and Jean-Luc Imler: critical reading of the manuscript.

S3: The tale(nt) of Hoffmann: examples

When Jules Hoffmann speaks in his seminars, he gives the impression that he is quite detached, with a distant perspective of the actual work. The research is described as an epic involving many protagonists in which the works of individuals becomes lost in the haze. Acknowledgements and any credit go in priority to members known to be fully devoted to the 'chief' rather than to those who actually did the work. In a way, this is reminiscent of the story about an army general, who always stays two men away from the battle.

This type of speech has probably a lot to do with the old French hierarchical system in science but may also be observed with PIs who have lost the contact with reality due to excessive travels or commitment to administration. Below I have provided a two examples.

S3A: Seminars

In seminars, Jules Hoffmann never mentions my contribution as the key step. The story is described as an « epepee » ("epic") that started a long time ago and my contribution, i.e. the one that has made him famous and got him the Nobel prize, is never really acknowledged. I am usually cited in a general acknowledgement with the photos of all the other lab members at the end of the talk. He also adapts his talk to the audience. For instance, in this NIH (National Institutes of Health) seminar (**see time period 10min-14min30 in <http://videocast.nih.gov/summary.asp?file=16749>**): the use of "we" in the key work on Toll and Imd pathways. What is odd is the way he quotes all the co-authors on the paper, even though many of them had a rather minor role. However, this talk is probably one of his most favorable to me, since my name is at least associated with Toll in the acknowledgements! Needless to say the students are rarely, or never mentioned.

S3B: Another example:

A telephone interview with Jules A. Hoffmann following the announcement of the 2011 Nobel Prize in Physiology or Medicine. The interviewer is Adam Smith, Editorial Director of Nobel Media.

[AS] Well, let's turn to immunity then. You were awarded the Nobel Prize for your discovery that Toll was the sensor of innate immunity in the fly. What started you studying immunity in flies anyway?

[JH] Well, actually we started – it's a long story – Then, finally, at a given moment in 1990 or so, we decided with my colleagues – particularly Jean-Marc Reichhart and Charles Hetru here – we decided that we would go over to *Drosophila*. Also, no peptides had been identified yet. No effector molecules had been identified yet in flies. But we thought that we might be able to find something – we hoped we would be able to find something because we had, by that time, found in larger flies induction of antimicrobial peptides. And, so, we went ahead and then we went over to *Drosophila*. We hired in a *Drosophila* geneticist, Bruno Lemaitre, and later Dominique Ferrandon, and the team then became both biochemistry, cell biology, molecular biology and molecular genetics, and so on. Finally, at a given moment ... Well, the way we came to Toll was through the work of [Nüsslein-Volhard](#)

...

[AS] Of course, because she had identified it as a gene important in embryonic development, yes?

[JH] ... Yes. And what she had seen is that this activates Dorsal – and Dorsal is an NF-kappaB family member. And, we found that there were sites ... we found that there were, in the promoter sequences of the antimicrobial peptide genes, there were NF-kappaB binding sites, and then we could, through transgenesis experiments, we could demonstrate that those sites were mandatory, conductivity, and so, step-by-step, we worked up to ... But initially it was not something obvious that Toll – Nüsslein-Volhard had described Toll as being a maternally expressed gene – and now here we're working on adult flies, we were working on males, where there was no maternal effect involved. And so we first had to show that, really, the system was inducible in adult flies – adult males – and so on. And then this is what got us to find that this was an immune function for this cell receptor.

[AS] It very nicely illustrates the tremendous amount of background that lies behind a seemingly singular discovery such as Toll's role in innate immunity.

[JH] Yes.

This interview by Nobel Media is another good example of communication bias. Nothing is wrong, but at no point is it possible to distinguish that I did the work in a very independent manner. The scheme is again the description of an epic. My name is never mentioned at the key step when the Toll discovery is mentioned. The statement “we hired in a *Drosophila* geneticist, Bruno Lemaitre” is wrong since I went to the laboratory with my own fellowship the first year. There was no open position for a geneticist to my knowledge. This way of presenting the Toll story is rather surprising if we consider that Jules Hoffmann did not take much interest in the genetics approach while I started the work! Also very problematic, the contribution of Philippe Bulet is not mentioned at all. However it was his team that discovered the Drosocin, Drosomycin, Metchnikowin, and Defensin antimicrobial peptides (via HPLC purification), that was the compulsory initial step before we could even begin to investigate their regulatory pathways! Priorities in the text are clearly given to the faithful bodyguards.

Text S4: Invitations to immunology meetings.

It is very interesting to note how at the onset of the Toll-TLR story, communication has been monopolized by just a few speakers. This is especially true for *Drosophila* for which Jules Hoffmann became a real peddler. During the 10 years that followed the 1996 Cell paper, I was rarely invited to present at “immunology” meetings² especially at key meetings on innate immunity that were frequent at that time. I was certainly never invited to any meeting organized by Jules Hoffmann. Only in 2006 did I start to be regularly invited (Toll 2006, Salvador, Brazil) and got to know some of the protagonists in the vertebrate field. Perhaps my communication skills were considered too poor or my science too mediocre! Either way, it was too late to establish my own network! A good point is that I was less distracted from the lab bench. Nevertheless, being out of the gatherings, I did not realize how much Jules had transformed the Toll story into a team tale.

2: Meetings where I was invited

- World Congress on Trauma, Shock, Inflammation and Sepsis, Munich March 2000
- Société Française d’Immunologie, Paris , 29/11/2000
- 16th Naito Conference on innate immunity, Shonan Village, Japan October 2003
- European society for immunodeficiencies, ESID, Versailles, 21/10/04
- EMBO workshop in immunology, Marseille, January 2005.

Text S5 with FigS2

An analysis of Jules Hoffmann’s publications (extracted from [PubMed](#) and [Google Scholar](#))

This list of publications shows that almost all the publications associated with *Drosophila* immunity has come from work that was not directly directed by Jules Hoffmann. Publications from the 1993-1997 period (the time when Toll’s role in immunity was discovered) are indicated in yellow. Note the important contribution of Philippe Bulet’s team which is rarely acknowledged in any of Jules’ talks.