Nobel Prize credits criticised

Borrowed Plumes

Photo: Fotolia/ Yahia LOUKKAL

The 2011 Nobel Prize for Medicine or Physiology has been dogged by controversy. The only one of the three recipients not to be accused of unethical behaviour, Ralph Steinman, had the misfortune of dying before he could hear of his award for dendritic cells. Meanwhile, Jules Hoffmann and Bruce Beutler have since been accused of unfairly promoting their own contributions to these discoveries. Here, Jeremy Garwood, investigates the "case" of Hoffman, whereas Beutler is at the centre of an accompanying article at *Lab Times* online (*www.labtimes.org*).

Bruno Lemaitre, now professor at Lausanne's EPFL, says Jules Hoffmann took unjust credit for his discoveries concerning genetic regulation of innate immunity in *Drosophila*.

Fly credits and miscredits

In 1992, Lemaitre came to Hoffmann's CNRS laboratory in Strasbourg. He had just obtained his PhD in Paris. He was the only geneticist in the lab. His project was to study the genes regulating the expression of antimicrobial peptides. By the time he left Strasbourg, in 1998, to set up his own lab group, he had published three key papers describing the discovery of a new mutation, imd (immune deficiency), that regulated the immune response of flies to bacterial infection and had established that the gene, Toll, regulated the response to fungal infection. It is for the second of these three papers, Lemaitre *et al.* (*Cell,* 86(6):973-83) that Jules Hoffmann was awarded the Nobel Prize in 2011.

Lemaitre told *Le Monde* (10/12/11), "I'm disappointed that the jury chose a personality who was very far from the realities of experimental research, someone who knew how to gain personal benefit from discoveries made by other researchers. He does not correspond to my model scientist, who is closer to the lab bench and shows more respect for other people's work. The Toll story was the fruit of a complex adventure involving numerous laboratories. Scientific marketing and networking has certainly played a predominant role in attributing the credit."

Lemaitre has created a website (*www.behinddiscoveries.com*) where he presents extensive documentary evidence to support his claim. He had been wanting to protest for a long time but it was the award of the Nobel that finally precipitated his response, "I know some of you may think this is a little too late but this has not been easy for me."

I have already discussed the key points of Lemaitre's case elsewhere, in my LT online article "A Nobel Prize not Immune from Error?" (*www.labtimes.org/editorial/e_270.html*). In this current article, I will present the results of my own investigation into the research career and practices of Jules Hoffmann. At the end, you can judge for yourselves whether you think he merited the Prize.

The main accusation

"Subsequent to the publication of my Toll research (and my departure from the lab) Jules Hoffmann never gave me enough credit for it. I was informed of this by colleagues who heard his talks and confirmed this through my own personal investigations. Immunologists ought to understand just how far Jules Hoffmann was from the realities of experimental work. This is in total contrast to the enormous respect that I have for other members of the Strasbourg research institute who produced high quality research," Lemaitre wrote to *Science* magazine (*Science*, 'Nobel Prize for Immunologists Provokes Yet Another Debate' 16/12/11).

"In France," Lemaitre says, "it is hardly a secret that Jules Hoffmann has been mostly involved in networking and communication rather than a dedicated experimenter. He was far away from the bench work before, during, and after my work on Toll. To put it simply, he has been the wonderful

spokesperson for a fantastic lab but in reality, in the background, the good science and creative work was performed by other researchers. Moreover, his powerful place in the field makes him an unavoidable part of the domain. But is this really sufficient to win a Nobel Prize?"

The main point is that Jules Hoffmann claimed overall credit, not just for Lemaitre's discoveries but also for key results from other talented young researchers in the lab. He did this by promoting himself when presenting the results in conference meetings, seminars and written reviews. Lemaitre provides examples of this on his website. His main tactic was never to name individual researchers in association with their discoveries but instead to refer to an impersonal "group" effort. Published results are always the work of "this laboratory" – "we have", "we did", "our" research. The only name to retain is that of the lab director, presenting **his** version of the story.

Lemaitre explains how "in seminars, Jules Hoffmann never mentions my contribution as the key step. The story is described as an «épopée» ("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."

Uninvited

In addition, Hoffmann seems to have made sure that Bruno Lemaitre was not present to contradict him at meetings. In 1998, Lemaitre set up his own research group near Paris continuing to do highly respected research on immunity, yet, "During the ten years that followed the 1996 *Cell* paper, I was rarely invited to present at 'immunology' meetings, especially at key meetings on innate immunity that were frequent at that time. I was certainly never invited to any meeting organised by Jules Hoffmann." It was not until 2006, ten years after 'the' *Cell* paper, that Lemaitre was finally invited to Toll meetings where, at last, he could meet some of the main vertebrate immunologists.

To date, Jules Hoffmann has not replied to Lemaitre's accusations. He did not answer queries from the *Times Higher Education* when they wrote about the matter ('Hoffmann's Nobel input 'distant' from bench work' 15/12/11, 'Did Hoffmann take Nobel for the team?' 22/12/11), nor has he replied to ***Lab Times***' request.

Science magazine managed to get a few words when they phoned him. He told *Science* that Lemaitre had informed him of the website but that he has not visited it because colleagues warned him he might find it "distressing" ('Nobel Prize for Immunologists Provokes Yet Another Debate' 16/12/11).

I decided to investigate further. I found abundant evidence to support Lemaitre's description of Hoffmann as the lab's administrative director, rather than an active researcher. Other biologists have confirmed this view, including Pat Simpson (now Professor of Comparative Embryology in Cambridge), who had a fly research group from 1983-2002 at the nearby IGBMC in Strasbourg. She said Hoffmann was "more of

an administrator and communicator than a bench scientist. While he deserves credit for administering the unit, he should have highlighted Bruno's role in the research, as well as others, more forcefully." (*Times Higher Education* 15/12/11).

The strangest thing I found, however, was that Jules Hoffmann claims to have been actively involved in immunity research from the very start of his research career in 1963. I've read his PhD thesis and looked at his publication record – neither of them supports these 'recollections'.

"A long story"?

Jules Hoffmann gave a telephone interview to Nobel Media two days after the official announcement that he had won the Prize (05/10/11, *www.nobelprize.org*).

Interviewer: "What started you studying immunity in flies anyway?"

Hoffmann: "It's a long story – we started looking at antimicrobial defences in insects, initially in grasshoppers, in the 1960s. And the reason we did that was that I did my PhD in the laboratory, which was working on grasshoppers and grasshoppers were, at that time, still a very big plague in countries, which were administered by the British and the French. And, so, our laboratory was doing endocrine studies, that is to say transplanting endocrine tissues or organs from one insect to the next, when they noted that it was never infection coming up – never *opportunistic* infection coming up – without any special care being taken to avoid microbes in the environment; there were no aseptic conditions. My thesis supervisor suggested that I take up the question of what helps the insects fight infections. And so that's what, then, I did. And initially it was experimental biology with X-ray treatments and so on. And from there, we got into the biochemistry of the effector molecules and then we discovered the antimicrobial peptides and so on."

Photo: iStockphoto/ Coffee999

From locust endocrinology to *Drosophila* immunity in absolutely no time...

The 1960s bench scientist

Jules Hoffmann was born in 1941. He completed his undergraduate studies in Luxembourg in 1963, then moved to the University of Strasbourg, France. In 1964, having become a salaried CNRS scientist, he began his thesis (research jobs were a lot easier to get in those days!). Under the supervision of Pierre Joly, head of the Laboratory of General Biology (LGB), he obtained his PhD ('Docteur ès sciences naturelles') on 22nd September, 1969 (age 28).

Hoffmann's doctoral thesis was on blood cells in the locust ('Etude des cellules sanguines chez *Locusta migratoria*'). It is in two volumes with 102 pages of text (including bibliography) in the first and 51 photographs of locust blood cells in the second. In the introduction, he explains he is studying the postembryonic development of blood cells in order to understand more about how insect hormones regulate the physiology of the blood system (endocrinology).

His experimental work is divided into four parts. The first is a morphological study of locust blood cells using the optical microscope. He describes four different cell types.

The second part describes how he bled locusts – he removed up to 80% of their blood – in order to stimulate production of new blood cells that he then quantified under the microscope. In the third section, he looked for the blood cell-producing organs before and after he bled various locusts and crickets (*Gryllus bimaculatus*).

Finally, he looks at the endocrine control of blood cell production. However, this is still at a time when no one knew, which parts of the insect were actually producing the hormones, so Hoffmann's study involved insect surgery. He removed organs (the corpora allata, pars intercerebralis and corpora cardiaca) and looked to see if their absence had any effect on the insect's capacity to generate more blood. After his blood cell quantification, he concluded that the corpora allata had the most direct effect.

Early works

Hoffmann lists 14 articles he published from his doctoral work. These are all written in French and are mostly two to three page notes in French journals. However, only two of them can really be considered full research articles: *Z Zellforsch Mikrosk Anat,* 1970;106:451-72 and *Gen Comp Endocrinol,* 1970;15:198-219. In the latter, Hoffmann notes that cardiectomy (removal of the heart) only slows down the differentiation of two types of blood cell but that this is 'almost entirely blocked' when the locusts are not fed.

Nowhere in his PhD thesis is there any mention of infection, bacteria, or anything remotely resembling immunity. When the function of blood cells is mentioned it is with respect to insect development. For example, during insect moulting, blood cells phagocytose larval cells to make way for adult structures.

Why then does Hoffmann claim to have had links to immunity in the 1960s?

For example in 1993, as administrative director for the CNRS research lab, URA 1490 (previously the LGB), he edited its biannual activity report for the CNRS. Such official reports explain what research has been done during the previous two years, with a description of plans for future research. The 1993 report begins with a one page essay on the 'History of the Laboratory of General Biology'.

In the second paragraph, he says Professor Joly had noted that insects did not get

bacterial infections. "Curious to know the explanation for this antibacterial resistance, he gave Jules Hoffmann as subject for his thesis the study of blood cells and their role in immune defence." He then writes that with the help of Aimé Porte, a cytophysiologist, he discovered a reticulo-hematopoietic organ in the locust. "Selective irradiation of this tissue with X-rays had two dramatic consequences: the insects lost their capacity to resist bacterial infections and the moulting cycles were blocked in irradiated larvae." The same essay appears in the 1997 CNRS report (the lab was now UPR 9022).

A 1974 paper from Porte's lab did look at the development of the prothoracic gland after irradiation (but at the time the prothoracic gland had just been identified as the organ producing the moulting hormone, ecdysone – *Science,* 183(4124):529-30; *PNAS,* 71(3):793-6). Hoffmann is the third of four authors. No mention of infection. In another 1974 paper (*Gen Comp Endocrin, 22(4):489-98*), it is simply noted that irradiation-sensitive cells appear to be necessary for hormone transport and/or mode of action.

Grasshopper infections

In September 2011, when Hoffmann was awarded the Shaw Prize ('Asia's Nobel'), he wrote the 'Autobiography of Jules A. Hoffmann' (*www.shawprize.org* – 28/09/11). In it, we learn that "Professor Joly offered me a position with the French National Research Agency (CNRS) and I started studying the antimicrobial defenses in grasshoppers. During the studies which led to my PhD defence in 1969, I focused on the origin of blood cells in grasshoppers and discovered a well-developed blood-forming tissue (hematopoietic tissue) in the vicinity of the heart vessel. Selective X-ray treatment of this tissue resulted in a massive septicemia."

He then says that he went to Karlson's lab in 1973 "while our group in Strasbourg started analysing the biological and biochemical contexts of infections in grasshoppers."

In the CNRS magazine for December, there is a three-page article based on an interview with Jules Hoffmann (p. 6-8): "Who would believe that when the young student in natural science at Strasbourg university decided to do his thesis on the mechanisms of antimicrobial defence in locusts, he was going to revolutionise the understanding of innate immunity?" It seems "this choice of thesis was not due to chance." Indeed! Later he says, "Looking back, I sometimes regret that during all these years I neglected studies on the mechanisms of antimicrobial defence in favour of endocrinology." Similar quotes have appeared elsewhere in the press.

The insect endocrinologist

In 1973, four years after he completed his PhD, Hoffmann spent a year in Peter Karlson's lab in Marburg, Germany (salaried CNRS scientist, age 32). Karlson had discovered the insect hormone, ecdysone, in 1954. It was only in 1974 that the prothoracic gland was finally identified (elsewhere) as the organ secreting it.

This was the only time Hoffmann went to another lab to do research. Subsequently, he directed a research group that investigated insect endocrinology and ecdysone metabolism, publishing over 50 articles during the next 20 years.

Hoffmann's biography at the French 'Academie des Sciences' (founded 1666) makes no mention of any early interest in immunity. Perhaps it was written in 1992, the year Hoffmann became a Member. Instead, it notes that Jules Hoffmann's main scientific work was on the neuroendocrine control of development and insect reproduction. He looked at the "biosynthesis and metabolism of ecdysone, the steroid hormone controlling insect moulting. His

The 'PI' and the 'IP' argument

Some commentators, particularly from the US, have argued that even if Hoffmann and Lemaitre shared credit for the Toll discovery, Hoffmann should win as 'PI' (Principal Investigator). However, was he really a PI in the US sense? In the US, a PI is under enormous pressure to attract research funds, endlessly writing grant applications for their research projects. Besides funding scientific experiments, this money is used to directly pay the lab's graduate students, postdoctoral researchers and technicians.

In the French research system, CNRS scientists and university teacher-researchers have stable, salaried jobs. There is an annual block grant given to research labs based on the number of permanent researchers (although reforms since 2007 are changing this – see *LT* 01/08 and 02/08). PhD students receive government grants. Furthermore, Bruno Lemaitre actually financed himself during his first year in Strasbourg from student teaching/research grants he'd received in Paris.

Meanwhile, French research scientists have their own independent research projects, approved by the CNRS and in harmony with the lab unit's general theme.

This is not quite the same stressful pressure that a PI, at the head of a lab group in the US, or even the UK or Germany, must face. Indeed, the earliest mention of a successful research grant in Hoffmann's c.v. dates from 1995 - he shared ('co-coordinator') an HFSP grant with some big names from immunology: Charles Janeway (Yale), Alan Ezekowitz (Boston), Shunji Natori (Tokyo) and Fotis Kafatos (EMBL).

If instead of a scientific discovery we were talking about a patent dispute, the question of credit would be assessed on the basis of 'Intellectual Property' (IP).

In such a case, the legally binding judgement is often based on dated laboratory records of the experimental work. This determines who has made the discovery first and who, therefore, has the legal right to a patent and any subsequent commercial royalties.

Bruno Lemaitre says he still has all his Strasbourg lab books and many associated documents (for example, details of requests for fly mutations): "I still have all of my laboratory notebooks in my office with me – neither of my lab chiefs ever looked carefully at my data."

Not that there is a patent dispute about Toll. Instead, this is about fair credit and just recognition for good scientific research. However, Hoffmann may have benefited financially from his enhanced reputation. For example, would investors have otherwise been so willing to support 'Entomed', the company he founded in 1999? Entomed absorbed over 20 million euros of investors' money before going bankrupt in 2005.

And then there's all that prize money for his immunity research. Starting with the Coley in 2003 ($5,000), these included the Balzan (2007 - half of CHF750,000), Keio (2010 - half of ¥20 million), Shaw (2011, third of $1million) and Nobel (half of €600,000). Amazing what a good research reputation can do for you! But was it justified?

research led to the discovery of a maternal contribution of ecdysone in the form of phosphoconjugates and to the understanding of their function in the generation of the embryonic cuticle." This matches his publication record through to 1991 (age 50).

The real immunity link – His wife!

In fact, the Hoffmann that worked on insect immunity was Daniele, Jules Hoffmann's wife. Her research career is fairly modest. She started as a lab technician. In between having their two children (in 1970 and 1974), she obtained a position with the CNRS (1973) in the same lab and began doing research. In 1976, she first published a note on the 'Role of phagocytosis and soluble antibacterial factors in experimental immunization of *Locusta migratoria*', in which she says that larvae "can be protected ('vaccinated') against lethal doses of *Bacillus thuringiensis* by previous injections of low doses of this pathogen." (*C R Acad Sci Hebd Seances Acad Sci D,* 282:1021-4). That's to say, she was looking at the possibility of adaptive, not innate, immunity.

Photo: The Nobel Foundation 2011

Did he rightfully enjoy his "Lobster with pickled winter vegetables and Jerusalem artichoke purée" at the Nobel banquet in December?

Meanwhile, Sweden's Hans Boman, the researcher who really "wondered why insects exposed to pathogenic bacteria don't get ill", published his breakthrough report on "Inducible antibacterial defence in *Drosophila*" (*Nature,* 237:232-5). In 1981, Boman's lab was also the first to report the isolation of antimicrobial peptides from insects and presented the first sequenced peptides, cecropin A and B (*Nature,* 292:246-8).

In 1979, Daniele Hoffmann duly went to Boman to learn techniques. Her next paper, in 1984, describes 'Detection of distant antigenic relationships between insect and bird lysozymes by ELISA' (*J Mol Evol,* 21:14-8).

It was around this time that some younger researchers started working with her. By 1988, they had purified, sequenced and cloned some antimicrobial peptides from Phornia (blow fly) larvae (*Eur J Biochem,* 171:17-22; *Eur J Biochem,* 182:423-7). Subsequently, their research group switched to *Drosophila*. Two key researchers at this time were Philippe Bulet, who purified a whole succession of novel antimicrobial peptides from *Drosophila*, and Jean-Marc Reichhart, who used molecular biology to look at their genes. This brings us to

1992 when Bruno Lemaitre arrived in the lab to do the first genetic analyses.

Hoffmann has told a story that seems to be at odds with the facts. Yes, he worked on insect blood cells, but his largely microscopic and physiological studies were all directed towards questions of endocrinology. Wouldn't it have been simpler (and more accurate) to have said something along the lines of: I worked on insect endocrinology for 30 years. In the mid-1980s, a small group in the CNRS lab that I directed began to make the first of a significant series of discoveries in insect immunity. In 1991, the rest of the lab agreed to switch from endocrinology research to insect immunity?

Why did he feel the need to tell a modified tale from 1993 on? Was the story for vertebrate immunologists with whom he had begun to establish contacts?

Perhaps it doesn't really matter that he claims an active involvement in immunity research since 1963. But what other details might have been adjusted to present himself in a more favourable light?

The administrator

In 1978, Jules Hoffmann succeeded Pierre Joly as administrative director of the Laboratory of General Biology. This was a 'mixed' lab, combining teacher-researchers from the University of Strasbourg and full-time CNRS researchers. His research group continued to make advances in their studies of ecdysone biochemistry and insect endocrinology. However, it seems unlikely that Jules Hoffmann did much experimental work himself, and for cause! A look at his c.v. reveals that he took on a considerable number of administrative tasks outside the lab.

For example, he was often in Paris, either as a member of the CNRS Life Sciences steering committee (1983-91/1995-2000) or as President of the CNRS national committee controlling Developmental Biology researchers and their activity (1983-91/1995-2000); he was also on the Research council of the Ministry of Higher Education and Research (1994-97). Within the University of Strasbourg, he directed the DEA courses in cellular and molecular biology (one-year research diplomas that select future PhD students) from 1990-2002. And there's the international travel – a list of CNRS-approved official conference 'missions' includes: 40 trips to the US (10 months in total), Germany (20 trips, 6 months), the UK (15 times, 2 months), China (12, 2 months), Japan (15, 2 months), Canada (8), Russia (6), etc.

In 1993, his renamed CNRS lab, 'UPR 9022' ('Insect immune response and development') had grown to 30 'statutory' staff (i.e. with permanent jobs) – 9 CNRS researchers, 6 university teacher-researchers, 5 research engineers and 9 technicians. There were also 4 PhD and 9 DEA students. In the same year, he became director of the CNRS Institute of Cellular and Molecular Biology (IBMC), incorporating two other CNRS labs (UPR 9002 and 9021), all under his overall administration.

A fateful meeting of two men who are not without their controversies, King Carl XVI Gustaf of Sweden (right) and Jules Hoffmann (left).

Last author credits

Lemaitre admits he was naïve about the co-author question, "It did not seem important to me since I was obviously the first author." Some journals now ask authors to briefly explain their contribution to research articles. This was not the case then but Lemaitre now details the respective roles of his four co-authors (text S2 on his website).

He states that he "ordered the Toll pathway mutant lines, designed all the experiments, organised the work with other people, analysed all the experiments, and wrote the paper". Meanwhile, the two PhD students, Emmanuelle Nicolas and Lydia Michaut (2nd and 3rd authors), aided with his Northern blots; Jean-Marc Reichhart's name appeared 4th as group leader, and Hoffmann helped write the final version of the manuscript (last author).

By a cruel irony, it was at around this time that the lab's perception of 'last author' status changed. Prior to 1996, Hoffmann appears as last author on many papers where closer inspection suggests he was not the main researcher. For example, Philippe Bulet's PhD student, Pascale Fehlbaum, published two important articles on antimicrobial peptides (*J Biol Chem,* 269(52):33159-63; PNAS, 93(3):1221-5). Yet Bulet, 'PI' on peptide purification since 1991, only appears as 2nd author, while Hoffmann is last. After this date, the 'PIs' appear to have asserted their rights – Lemaitre was senior author when his stu-

dent, Emmanuelle Nicolas, published her two papers. Subsequently, Hoffmann is in before last position.

Why weren't the French researchers more concerned before? Perhaps because the order of authors did not have the same significance it had acquired elsewhere. They already had stable, permanent research positions. Besides, the CNRS did not use 'bibliometry' to judge their activity until later. Sure, they had to publish papers for promotions but the order of authors was not so important. How times have changed!

Re-interpreting history?

When he received the Shaw Prize, Hoffmann wrote, "It goes without saying that the scientific achievements of our laboratory over the many years, as recounted above, are to be credited to a long list of collaborators of high intellectual and human calibers." But he never does quite manage to say who they are!

One week later, Jules Hoffmann learned he had been awarded the Nobel Prize for Bruno Lemaitre's 1996 *Cell* paper. Instantly, he tried discussing the participation of Lemaitre in the Toll discovery.

It wasn't easy for him.

In his Nobel Media interview, two days later, he recounts "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 ..." (Christiane Nüsslein-Volhard had already won the Nobel Prize in 1995).

Initially, he told the French press, "With notably Bruno Lemaitre and Jean-Marc Reichhart, we found a receptor, a molecule, that recognised substances common to many bacteria." (*Le Monde* 4/10/11). By December 2011, he had decided that "with Bruno Lemaitre, we succeeded in showing that the receptor Toll..." (Le Point 14/12/11).

Meanwhile, JM Reichhart accused Lemaitre of "re-interpreting history" (*Science* magazine 16/12/11). But Reichhart agreed that Hoffmann was indeed a skilled communicator, "If he had been less talented at telling the Toll story, the Nobel Prize would not have happened at all! You have to tell the people what you have discovered. Jules is a very good ambassador for the field of innate immunity."

Lessons learned

Reichhart succeeded Hoffmann as head of the CNRS lab in 2006. He appears to have learnt a thing or two. In his research profile (on the IBMC website), he explains how in 1992 he became interested in *Drosophila* embryonic development and the formation of the dorsoventral axis, "In 1996, this led **me** to the Toll discovery (Lemaitre *et al. Cell* 1996)..." No mention of Hoffmann there!

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