

## Portrait of Brigitte Kieffer

## The importance of a connective science



Brigitte Kieffer is a research director the French at National Institute Health and of Medical Research (Inserm) at the Strasbourg Centre **Biomedical** for Research (CRBS). Her work on opiate receptors paved

the way to understanding the analgesic and addictive effects of substances such as morphine. Today, she aspires to understand the long-term effects that exposure to opiates has on neural networks and is committed to improving dialogue between the fields of biology and psychiatry.

She has been awarded the Paul Ehrlich Chair in the life sciences at the University of Strasbourg Institute for Advanced Study (USIAS), for the 2022-2024 period.

A neurobiologist for more than 30 years, Brigitte Kieffer is interested in the mechanisms related to pain and reward in the brain. The capacity of nature to achieve extraordinary things led to her decision to study biology. "I was enthralled when the genetic code was explained to me for the first time," she remembers. Soon after, she became fascinated by the brain and the nervous system and turned her attention to neuroscience. During her thesis, she identified the acetylcholine binding site on an enzyme called acetylcholinesterase, which is involved in transmitting information between nerves and muscles. She then embarked on postdoctoral research at the Friedrich Miescher Institute for Biomedical Research, in Basel (Switzerland), where she worked on another subject entirely. Between 1986 and 1987, in the midst of the molecular biology boom, she became intrigued by the rapid development of gene cloning and took the opportunity to acquire as much knowledge as possible about this approach.

It was with this background that she became a lecturer in Strasbourg and looked at opiates and their receptors which, in the nervous system, allow substances such as morphine or heroin to exert a painkiller effect whilst simultaneously creating addiction. At that time, no one had yet succeeded in isolating these receptors, even though many laboratories around the world had been trying to do so for a good decade. Having identified this gap, she set off to fill it. In 1992, inspired by cloning methods used widely in immunology, and calling upon her skills as a biochemist and her knowledge of cloning techniques, she managed to isolate and clone the gene coding for the delta receptor with her colleagues Claire Gavériaux-Ruff and Katia Befort. *"I couldn't believe it,"* she recalls. *"It was so incredible that I had to repeat the operation several times before realising that we had succeeded."* 

This was a major breakthrough in their field. Indeed, once a gene is isolated and sequenced, it becomes possible to look for its relatives. Therefore, after delta, the mu and kappa receptors also revealed their secrets and biologists were subsequently able to study and understand the signalling paths associated with these molecules. Today, their structure is known at the atomic scale. This discovery became the cornerstone for a number of subsequent research projects on opiates and the way in which they suppress pain and create addiction.



In the following years, Brigitte Kieffer started to study opiate receptors in the brain of mice, an animal model in which the genome can be accessed in vivo and whose behaviour can be studied live. One of her recent goals is to understand the modifications that occur in the abstinent subject – i.e. one chronically exposed to an opiate before being weaned off it – and to uncover why relapse is almost unavoidable. Her focus is less on the physical effects of withdrawal and more on the negative affect of opiate abstinence, like mood disorders and negative emotions, similar to what occurs in depression and which it is difficult to fight against. In particular, she wants to shed light on which cerebral region these mechanisms are rooted in, and on the neuronal networks involved. In order to do so, she collaborates with scientists with different and complementary expertise; a work philosophy oriented towards the transversality of domains and a perpetual quest to acquire new skills.

## "Good exploration is when, more than just understanding how neurons work as cells, we try to grasp their complexity of their connectivity with all of the neural networks in the brain."

She also highlights the importance of not working in isolation. "In the field of neurobiology, one can work at the molecular level (genetic, epigenetic), at the neural level (cell signalling, physiology) or at the systematic level (brain, behaviour), and the greatest challenge is to integrate all of this information. It requires collaboration between disciplines that are very different."



In this regard, Brigitte Kieffer wants to build bridges and improve dialogue between neurosciences and psychiatry. For her, this constitutes one of the next big steps in her field. Many pharmaceutical companies have progressively phased out their neuroscience departments because of poor results and repeated failures. As a result, psychiatry is about 20 years behind when compared to the progress that is seen in, e.g. oncology, because it is very difficult to analyse the biology of the brain. Reducing the gap between neurosciences and mental health is crucial – a gap that she personally experienced when she was head of the Douglas Institute, in Montreal, Canada. The problem is that a psychiatric pathology is defined by complex psychological criteria, notably based on the analysis of a patient's behaviour and perception.

However, such criteria hide cerebral malfunctions that probably vary a lot from one case to another. Strictly speaking, there are unfortunately no biological criteria that can be used to define a mental disorder. And yet, uncovering such biological markers would be of great help in developing new, efficient drugs and in customising therapeutical approaches. There is no doubt in her mind that a better collaboration between disciplines will nurture progress in mental health.

## "Dialogue with the public is also very important, although it can be quite difficult"

Brigitte Kieffer adds. "For a scientist, nothing is ever really simple, so explaining things simply can lead to saying something inaccurate, false, or even unintentionally misleading." But, drawing on 15 years of teaching at the university and on the hundreds of conferences that she has given all around the world to diverse audiences, she is glad to engage in this important process.

Brigitte Kieffer is the first to hold the Paul Ehrlich Chair in the life sciences at the University of Strasbourg Institute for Advanced Study (USIAS), between 2022 and 2024. This chair is named after the German scientist of the same name, who studied at the University of Strasbourg and who won a Nobel prize in physiology in 1908. It showcases life scientists from Strasbourg who have made outstanding contributions to their field. She is proud to have been nominated and honoured to be recognised by the university where she has studied and worked for many years. She particularly appreciates the great freedom that comes with the chair.

"I want to take advantage of this opportunity to do what's most interesting in research, meeting with colleagues and learning new things that enrich my own research, thereby further building the connections that are crucial for progress."

Interview by William Rowe-Pirra, science journalist



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