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Fluorescent peptide biosensors for probing kinase activities: New tools for cancer diagnostics and drug discovery

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Cyclin-dependant kinases (CDK/cyclins) constitute a class of heterodimeric kinases whose members play a central role in coordinating cell cycle progression and participate in a wide variety of essential biological processes including transcription, neuronal differentiation and metabolism. These kinases are frequently hyperactivated in cancer cells and contribute to sustain unrestrained proliferation, thereby constituting established cancer biomarkers and attractive pharmacological targets for anticancer therapeutics. However, despite the oncological relevance of CDK/cyclin kinases, there are very few means of quantifying their relative activities to identify their hyperactivation. In order to monitor the activity of these kinases in complex biological samples, such as cell extracts, tissue or tumor biopsies and develop sensitive tools for diagnostic purposes, we have developed a toolbox of fluorescent biosensors through conjugation of environmentally-sensitive probes to synthetic modular polypeptides derived from kinase-specific substrates. These non-genetic biosensors offer a straight forward means of sensing subtle alterations in kinase activity in real time, in vitro and in living cells following facilitated delivery by cell-penetrating peptides. These selective chemical probes allow to quantify differences between healthy and cancer cell lines and in response to therapeutics. This technology is further suitable for probing and alterations in kinase activities in living cells as well as in tissue samples and tumor biopsies. In particular, we have engineered a CDK4/Cyclin D-specific biosensor which we have implemented to quantify CDK4/Cyclin D activity in healthy and pathological skin biopsies and a CDK5/p25-specific biosensor which provides means of monitoring this kinase in neuronal cells and assessing its hyperactivation in neuronal disorders such as glioblastoma. Taken together, these fluorescent biosensors constitute attractive tools for cancer diagnostics, for monitoring cancer progression and evaluating response to therapeutics, whilst also enabling development of sensitive assays for high throughput screening and offering promising perspectives for drug discovery.

Biography

May C Morris has obtained her PhD in Biology and Health Sciences at the University of Montpellier, France in 1997 and completed her Postdoctoral training at the Scripps Research Institute, La Jolla, USA. In 2000, she was hired by the CNRS and returned to the Centre of Research on Macromolecular Biochemistry in Montpellier, France. In 2005, she established her own research group and she was promoted to CNRS Research Director in 2010. In 2014 she moved to the Institute of Biomolecules Max Mousseron, where she is currently In-Charge of the Biosensors and Inhibitors group within the Department of Amino Acids, Heterocycles, Peptides and Proteins for Health. She was awarded the CNRS Bronze Medal in 2006 and the Scientist of the Future award from Languedoc-Roussillon Region in 2009. She has published over 65 articles in peer-reviewed journals, 18 chapters in books and 8 patents, edited a volume on *Fluorescent Biosensors* (Elsevier Press) in 2013 and a special issue on Fluorescent Biosensors in *Biotechnology Journal* in 2014. She is currently an Editorial Board Member of *ChemBioChem* and *Frontiers in Chemistry*.

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