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Fluorescent Biosensors for Probing Protein Kinases

Juan Antonio González-Vera

*IEF Marie Curie Researcher in Institut des Biomolécules Max Mousseron, IBMM-CNRS-UMR 5247,
Faculté de Pharmacie, 15 Av. Charles Flahault, 34093 Montpellier, France*

Phosphorylation triggered by extracellular signals and carried out by protein kinases is a fundamental signal transduction mechanism involved in the regulation of most basic processes in eukaryotic cells. In particular, cyclin-dependent kinases (CDK/cyclins) play a central role in coordinating cell cycle progression, and in sustaining proliferation of cancer cells, thereby, constituting established cancer biomarkers and attractive pharmacological targets.¹ Unfortunately, diagnostic approaches for detecting alterations in these kinase activities in a standardized fashion are poorly developed, and they involve indirect and invasive approaches. Consequently, sensitive and selective tools for monitoring kinase activities are of great importance, not only in the process of drug discovery, but also for unraveling the diverse signaling cascades in which these enzymes are pivotal. Peptide-based biosensors that rely on fluorescence changes upon phosphorylation are highly desirable, because these systems allow a continuous readout, offering an excellent spatial and temporal resolution to observe in real time the kinase activity in a sensitive and non-invasive fashion.²

In this presentation, first, I will describe the development of fluorescent biosensors of protein kinase activity based on chelation enhanced³ and environment-sensitive⁴ fluorophores, as well as a lanthanide-based reporter to probe CDK4/cyclin D. Second, I will present the development of novel 4,5-quinolimide-based environment-sensitive fluorophores and its application to CDK5 probes.⁵

¹ Malumbres, M. *et al. Nat. Rev. Cancer.* **2001**, *1*, 222-231.

² a) González-Vera, J. A. *Chem. Soc. Rev.*, **2012**, *41*, 1652-1664. b) González-Vera, J. A. *et al. Proteomes*, **2015**, *3*, 369-410.

³ a) Luković, E. *et al. J. Am. Chem. Soc.*, **2008**, *130*, 12821-12827. b) González-Vera, J. A. *et al. Bioorg. Med. Chem. Lett.*, **2009**, *19*, 1258-1260. c) González-Vera, J. A. *et al. J. Org. Chem.*, **2009**, *74*, 7309-7314.

⁴ Prével, C. *et al. Biosens. Bioelectron.*, **2016**, *85*, 371-380.

⁵ González-Vera, J. A. *et al. Chem. Commun.*, **2016**, *52*, 9652-9655.