Designing Chemical Tools to Shed Light on G Protein-Coupled Receptors

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G-protein-coupled receptors (GPCRs) are the largest family of transmembrane receptors in humans and the targets of more than 30% of all known drugs on the market. The ability to detect, measure and quantify the binding of ligands to these receptors and the resultant responses both *in vitro* and *in vivo* represent key elements of the drug discovery process.

Owing to their sensitivity and to their reduced environmental safety risk, fluorescence technics represent powerful tools to investigate the function, dynamic and location of GPCRs. In this presentation, I will describe the design and the synthesis of original fluorescent GPCR ligands, combining organic synthesis,[1] medicinal chemistry and computational modeling.[2] These probes have found various applications in GPCR chemical biology and drug discovery, to set up new receptor-selective high-throughput screening assays,[3] to study the functional architecture of GPCRs, especially their ability to form heterodimers[2] and to detect those receptors in living cells[4] as well as in whole organism.[5]

References

[1] (a) Margathe, J. F.; Iturrioz, X.; Regenass, P.; Karpenko, I.A.; Humbert, N.; De Rocquigny, H.; Hibert, M.; Llorens-Cortes, C.; Bonnet, D. *Chem. Eur. J.*, **2016**, *22*, 1399-1405; (b) Karpenko, I.A.; Klymchenko A. S.; Gioria, S.; Kreder, R.; Shulov, I.; Villa, P.; Mély, Y.; Hibert, M.; Bonnet, D. *Chem. Commun.*, **2015**, *51,* 2960-2963.
[2] Hounsou, C.; Margathe, J. F., Oueslati, N.; Belhocine, A.; Dupuis, E.; Thomas, C.; Mann, A.; Ilien, B.; Rognan, D.; Trinquet, E.; Hibert, M.; Pin, J.P.; Bonnet, D. and Durroux, T. *ACS ChemBiol.*, **2015**, *10*, 466-474.
[3] Karpenko, I.A.; Margathe, J. F.; Rodriguez, T.; Hibert, M.; Durroux, T.; Bonnet, D. *J. Med. Chem.,* **2015**, 58, 2547-2552.
[4] Karpenko, I.A.; Collot, M.; Richert, L.; Valencia, C.; Villa, P.; Mély, Y.; Hibert, M.; Bonnet, D. and Klymchenko A. S. *J. Am. Chem. Soc*., **2015**, *137*, 405-412.
[5] Esteoulle, L.; Daubeuf, F.; Collot, M.; Riché; S.; Durroux, T.; Brasse, D.; Marchand, P.; Karpenko, Iuliia A.; Klymchenko, A.S.; Bonnet, D. *Chem. Sci.* **2020**, *11*, 6824-6829.