CHEMICAL TOOLS FOR THE STUDY OF PROTEINS IN BIOLOGICAL SYSTEMS

Description

The Laboratory of Medical Chemistry of the Complutense University of Madrid (MedChemLab) carries out research projects based on the development of new therapeutic strategies aimed at the achievement of effective treatments for diseases of high incidence. The approach of this ambitious objective is structured from the perspectives of medical chemistry and biological chemistry.

One of the most important current problems in the development of new drugs is the lack of new therapeutic targets. In this sense, and with the challenge of identifying new therapeutic targets, a combination of biological and proteomic chemistry techniques has been put in place, allowing the in situ study of biological systems of greater complexity revealing expression profiles and protein activity.

Thus, the technology developed in the research group allows the obtaining of probes based on the ligands of interest that allow the in situ study in native systems (localization, expression levels, etc.) of the target proteins. In addition, a mass spectrometry based platform has been developed, which, together with the appropriate chemical probes, allows the identification of targets or the determination of de novo selectivity profiles of the ligands of interest.

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How does it work

Development of probes for the labeling of compounds.

The human proteome, designated as such the totality of proteins present in humans, has the ultimate responsibility for the correct functioning of the organism as a whole. In this way, any alteration in its activity, whether by default or by excess, leads to the appearance of pathologies.

Recent studies have shown the need for direct observation of the proteins that constitute pharmacological targets under physiological conditions as possible. To this end, bioconjugation techniques (such as the use of the avidin-biotin or streptavidin-biotin pair), modular and orthogonal chemistry (Staudinger ligation, cycloaddition [3 + 2]) and the use of fluorophores have been developed.

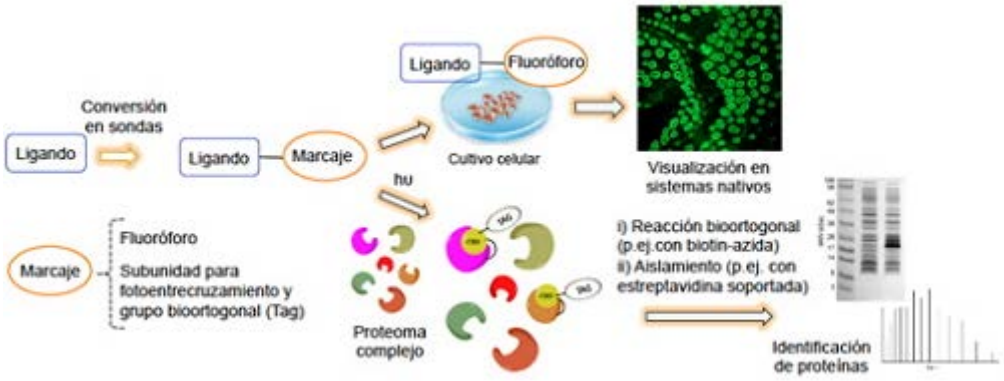
Therefore, the methodology developed jointly apply these techniques allowing the obtaining of probes based on the ligand of interest with different functionalities (fluorescence labeling, affinity or cross-linking) in order to obtain global information that would be impossible to infer by traditional methodologies .

Development of a platform for *de novo* analysis of ligand selectivity using mass spectrometry.

Traditionally the selectivity profiles of the compounds are performed considering the structural similarity, such that an active compound in a receptor is systematically analyzed in the rest of recipients of the same family. The fundamental limitation of this methodology resides, therefore, in that it assumes a prior knowledge of structural similarity. However, recent studies show that proteins with a high degree of structural similarity carry out completely different functions in vivo and, conversely, very different proteins structurally can carry out similar functions and act by similar mechanisms. Additionally, similarities in primary structures do not necessarily correlate with similarities in tertiary structures responsible for ligand recognition. Thus, the need for a methodology that reveals the complete selectivity profile of a de novo compound is evident. In this context, the methodology developed in the research group allows analyzing the de novo selectivity profile of a compound in a complex proteome, using mass spectrometry techniques.

Advantages

The competitive advantages that would contribute to a company the incorporation of the technology developed and / or under development in the Laboratory of Medical Chemistry is fundamentally the access to a methodology capable of establishing new *de novo* selectivity profiles and identifying new therapeutic targets.



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Where has it been developed

The present work is developed in the Laboratory of Medical Chemistry (MedChemLab) located in the Department of Organic Chemistry of the Faculty of Chemical Sciences of the Universidad Complutense de Madrid. The research team is led by Professor María Luz López Rodríguez and composed by the professors Bellinda Benhamú Salama and Silvia Ortega Gutiérrez, the professors contracted Mar Martín-Fontecha Corrales and Angeles Canales Mayordomo, two postdoctoral researchers, four predoctoral researchers, two Students of masters, two students of degree, two Erasmus students and a technician. The group includes researchers with different areas of specialization (organic chemistry, medical chemistry, biochemistry, cell and structural biology and molecular modeling).

The laboratory has all the equipment and instrumentation of a modern laboratory of organic chemistry and biological chemistry, necessary to carry out all the experiments of the different programs of medical chemistry in development. Robotic purification systems, microwave reactor, hydrogenation systems, polarimeter, infrared, ultraviolet and fluorescence spectrometers and a high efficiency liquid chromatography coupled to mass spectrometry are available. We also have access to the different Research Support Centers (CAI) of the UCM of nuclear magnetic resonance, proteomics, microanalysis, X-rays, electron microscopy, cytometry, etc.

The solid trajectory of the research group is reflected in the funding of 14 projects financed by public entities and private companies (UCB Pharma, Italfarmaco, Vivia Biotech) in the last 10 years, as well as in its scientific productivity. During the last 5 years, 36 articles have been published in the most prestigious journals in the areas of medical chemistry and biological chemistry (Nature, Nat. Commun., Nat. Neurosci., J. Natl. Cancer Inst., Angew. Chem. Int. Ed., J. Am. Chem. Soc., Allergy Clin. Immunol., Proc. Natl. Acad Sci. USA, J. Neurosci., Chem. Commun., Oncotarget, Breast Cancer Res. Int J. Cancer, Chem. Eur. J. Med. Chem., ACS Chem. Biol., J. Biol. Chem.), With an average impact index of 10.82.

Among the most relevant contributions of the last 10 years are the contribution to the study of the G protein-coupled receptors (GPCRs), in particular the clinical phase progression of several 5-HT1A agonists in collaboration with SchwarzPharma and UCB Pharma (4 patents And 9 articles in J. Med. Chem.); The identification of a new type of cannabinoid receptor located in mitochondria (5 articles in Science, J. Neurosci., J. Biol. Chem., Nat. Neurosci. And Nature); The validation of the FASN and ICMT enzymes as new targets for the treatment of cancer (2 international patents and 7 articles in Clin. Cancer Res. Breast Cancer Res., J. Med. Chem., Int. J. Cancer and Oncotarget.) ; The validation of the MAGL enzyme in the treatment of multiple sclerosis (an article in Angew. Chem. Int. Ed.) and the development, together with Vivia Biotech, of a powerful allosteric modulator of the GLP1 receptor for the treatment of type diabetes 2 (two patents).

And also

Partners are sought from public or private organizations related to the pharmaceutical industry and interested in the identification of therapeutic targets.

Responsible Researchers

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