University of Birmingham

Dr Youcef Mehellou

Lecturer in Medicinal Chemistry

Pharmacy and Therapeutics

Contact details

Telephone +44 (0)121 414 7024 (tel:+44 121 414 7024)

Email y.mehellou@bham.ac.uk (mailto:y.mehellou@bham.ac.uk)

School of Clinical and Experimental Medicine
College of Medical and Dental Sciences
University of Birmingham
Edgbaston
Birmingham
B15 2TT
UK

About

Youcef is a lecturer in Medicinal Chemistry and is actively involved in the development of the Medicinal Chemistry course that forms an integral part of the new Master of Pharmacy (MPharm) undergraduate degree programme within the College of Medical and Dental Sciences.

Youcef's teaching and research interests are focused on Biological and Medicinal Chemistry. In terms of teaching, Youcef teaches numerous courses that include chemical and biological properties of drug molecules as well as drug design and synthesis. As for research, Youcef's research is concerned with the use of chemistry to identify new drug targets and the design, synthesis and development of new small molecule therapies.

Youcef has published numerous papers that cover drug design and synthesis, protein engineering and the decoding of cell signalling in health and disease.

Qualifications

- Ph.D in Medicinal Chemistry (Cardiff University)
- MPharm (King's College London)

Biography

Youcef took up his position as a Lecturer in Medicinal Chemistry on the 1st March 2013.

Prior to this, Youcef was an MRC Career Development Fellow with Prof. Dario R. Alessi (FRS) at the MRC Protein Phosphorylation and Ubiquitylation Unit (MRC PPU), University of Dundee. While in this position, Youcef's work was concerned with the regulation of the catalytic activity of kinases, particularly SPAK, OSR1 and MSTs, by the scaffolding protein MO25. To this end and in collaboration with Prof. Stfan Knapp (University of Oxford), Youcef solved the crystal structure of the kinase MST3 in complex with MO25, which shed some light on the activation of kinases by MO25. Youcef also worked on developing highthroughput screening assays for identifying small molecules that inhibit various components of the WNK signalling pathway of which SPAK and OSR1 kinases are part of.

Before joining the Alessi lab, Youcef was a postdoctoral research associate with Prof. Sidney M. Hecht at the Biodesign Institute, Arizona State University, USA. Youcef's work then was on the development of chemical strategies that allow the incorporation of unnatural amino acids into proteins. While working on this project, Youcef developed a novel, simple and neat strategy for synthesising the unnatural amino acid thiothreonine, which was subsequently incorporated into proteins to study their biochemical and biophysical properties.

Youcef obtained his Ph.D. from the Welsh School of Pharmacy, Cardiff University. Youcef's postgraduate research was carried out in the laboratory of Prof. Christopher McGuigan. The project was on the design, synthesis and development of nucleoside analogues and their phosphate prodrugs (Phosphoramidates) as potential antiviral and anticancer therapies. During this work, Youcef synthesised a large number of nucleoside analogues and their phosphoramidate derivatives and explored their potential as antiviral and anticancer compounds in collaboration with Prof. Jan Balzarini. Youcef used molecular modelling as well as NMR studies to investigate the differences in biological activities seen with some of the nucleoside analogues phosphoramidates.

Before joining Prof. McGuigan's lab at Cardiff, Youcef was at King's College London where he did his MPharm degree. While there, Youcef did his MPharm project with Prof. Robert C. Hider and worked on the development of small molecule iron chelators as possible treatments of Alzheimer's and Parkinson's diseases.

Teaching

- MPharm Medicinal and Pharmaceutical Chemistry course
- Chemical and biological properties of drug molecules
- Design, synthesis and optimisation of drug molecules

Postgraduate supervision

- Evolution of new classes of siRNAs as potential therapeutics.
- Small molecule kinase inhibitors as potential treatments of hypertension.
- Building synthetic microtissues in vitro.

Research

Youcef's current research interests are focused on understanding and manipulating cell signalling through chemistry to identify new drug targets and develop new drug molecules.

Particular interests are in :

The design, synthesis and development of small molecules that interrupt certain kinases' activities in cells and thus offer a therapeutic potential. Kinases of current interest are those belonging to the WNK signalling pathway, e.g. WNK1, WNK4 and SPAK, which is involved in regulating blood pressure.

Also, the manipulation of cell signalling with siRNAs and synthetic microRNAs is another area of research interest to Youcef. The aim here is to introduce chemical modification to the nucleotides making up the siRNAs/microRNA in order to improve their in vivo stability and drug-like properties to increase their cellular uptake. Such reagents will make it possible to have stable and "transfection- reagents-free" short nucleic acids that control a wide range of cellular processes that play key roles in various diseases and conditions such as cancer, diabetes and viral infections.

Using chemistry to build synthetic microtissues in vitro in 3-D shapes that mimic how they are present in vivo is an area of great interest to Youcef. This Synthetic Biology initiate would allow the generation of synthetic microtissues in 3-D shapes that can be manipulated in vitro in a controlled manner to study many biological processes, e.g. cell-cell communication and stem cell development.

Youcef's research is interdisciplinary as it crosses many disciplines that include synthetic chemistry, molecular biology and biochemistry.

Publications

Ohta, A., Schumacher, F.R., Mehellou, Y., Johnson, C., Knebel, A., Macartney, T.J., Wood, N.T., Alessi, D.R., Kurz, T, 2013, The CUL3-KLHL3 E3 ligase complex mutated in Gordon's hypertension syndrome interacts with and ubiquitylates WNK isoforms; disease-causing mutations in KLHL3 and WNK4 disrupt interaction. Biochem. J., In Press doi:10.1042/BJ20121903.

Mehellou, Y., Alessi, D.R., Macartney, T.J., Szklarz, M., Knapp, S., Elkins, J.M., 2013, Structural insights into the activation of MST3 by MO25, Biochem. Biophys. Res. Commun. 431, 604-609.

Chen, S., Fahmi, N.E., Nangreave, R.C., Mehellou, Y., Hecht, S.M., 2012, Synthesis of pdCpAs and transfer RNAs activated with thiothreonine and derivatives. Bioorg. Med. Chem. 20, 2679-2689.

Thastrup, J.O., Rafiqi, F.H., Vitari, A.C., Pozo-Guisado, E., Deak, M., Mehellou, Y., Alessi, D.R., 2012, SPAK/OSR1 regulate NKCC1 and WNK activity: analysis of WNK isoform interactions and activation by T-loop trans-autophosphorylation, Biochem. J. 441, 325-337.

Filippi, B.M., de los Heros, P., Mehellou, Y., Navratilova, I., Gourlay, R., Deak, M., Plater, L., Toth, R., Zeqiraj, E., Alessi, D.R., 2011, MO25 is a master regulator of SPAK/OSR1 and MST3/MST4/YSK1 protein kinases. EMBO J. 30, 1730-1741.

Mehellou, Y., Valente, R., Mottram, H., Walsby, E., Mills, K.I., Balzarini, J., McGuigan, C., 2010, Phosphoramidates of 2'-beta-D-arabinouridine (AraU) as phosphate prodrugs; design, synthesis, in vitro activity and metabolism. Bioorg. Med. Chem. 18, 2439-2446.

Mehellou, Y., Balzarini, J., McGuigan, C., 2010, The design, synthesis and antiviral evaluation of a series of 5-trimethylsilyl-1-beta-D-(arabinofuranosyl)uracil phosphoramidate ProTides, Antivir. Chem. Chemother. 20, 153-160.

Mehellou, Y., Balzarini, J., McGuigan, C., 2009, An investigation into the anti-HIV activity of 2',3'-didehydro-2',3'-dideoxyuridine (d4U) and 2',3'-dideoxyuridine (ddU) phosphoramidate 'ProTide' derivatives. Org. Biomol. Chem. 7, 2548-53.