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Conferencia:

Sugars Shapes & Peptide Folds: Synthetic Mimetics to Modulate Protein Function

Aloysius Siriwardena

Laboratoire des Glycochimie, des Antimicrobiens (CNRS) & Université de Picardie Jules Verne, Amiens, France

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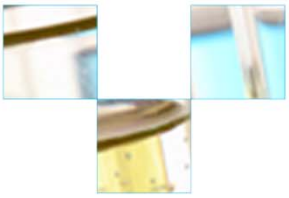

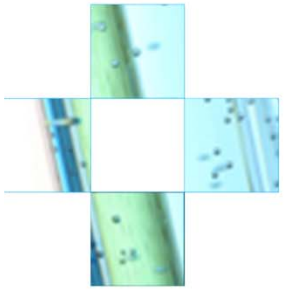

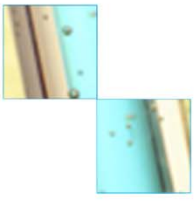

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Education

B. Sc. University of London, (1982)
Ph. D. University of London, UK (1986)
HDR Université de Picaride Jules Verne, (2006)

Positions Held

Postdoctoral Fellow: University of Munster, Germany (1987 - 1998)
Postdoctoral Fellow: Institut de Chimie de Substances Naturelles, (1999-2000)
Charge de Recherche, CNRS, Institut de Chimie des Substances Naturelles, Gif-Sur-Yvette, & Ecole Polytechnique, Lozere, France (2000-2004)
Visiting Scientist, Complex Carbohydrate Research Center, Athens, Georgia, USA (2000- 2004)
Professor of Chemistry & Biochemistry, University of Mississippi, Oxford, MS, USA (2002- 2004)
Charge de Recherche, CNRS, LG2A, , Amiens, France (2005-)

Sugars Shapes & Peptide Folds:
Synthetic Mimetics to Modulate Protein Function

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It is predicted that over half of all eukaryotic proteins are glycosylated and it is now established that co- and post-translational modification of proteins with glycans can have dramatic consequences on their folding, stability, and ultimately, their function.
Considerable effort has then not surprisingly been invested in delineating the impact of appended carbohydrates on the conformational preferences of proteins and peptides in solution and *vice versa*.

It has been shown that important insights into the functioning of proteins and of glycopeptides can be gleaned from the study of carbohydrate mimetics and that the interactions of these mimetics with cellular targets can impact a wide range of physiological phenomena.

In this presentation we describe our efforts in the synthesis of a number mimetics designed as chemical probes with which to better understand protein-glycan interactions. We have been particularly interested in understanding using these, the interactions of glycans with their cognate receptors (lectins) as well as the modes-of-action (and modes-of-inhibition) of catalytic proteins (glycosidases and glycosyl transferases) responsible for the biosynthesis of glycans.

For a selection of references see:

[1] A. Siriwardena, K. K. Pulukuri, P. S. Kandiyal, S. Roy, O. Bande, S. Ghosh, J. M. Garcia Fernàndez, F. Ariel Martin, J.-M.Ghigo, C. Beloin, K. Ito, R. Woods, R. S. Ampapathi, T. K. Chakraborty, *Angewandte Chemie. Int. Ed.,* 2013, 52, 10221
[2] A. J. Thompson, J. Dabin, J. Iglesias-Fernández, A. Ardèvol, Z. Dinev, S. J. Williams, A. Siriwardena, O. Bande, C. Moreland, T-C. Hu, D. K. Smith, H. J. Gilbert, C. Rovira, G. J. Davies, The Reaction Coordinate of a Bacterial GH47 alpha Mannosidase: a combined Quantum Mechanical & Structural Approach, *Angew. Chem. Int. Ed*, 2012, 51, 10997
[3] J. Gonzalez-Outereirino, J. Glushka, A. Siriwardena, R J. Woods. The Structure and Conformational Behavior of Sulfonium Salt Glycosidase, *J. Am. Chem. Soc*., **2004**, *126*, 6866.
[4] K. Karaveg, A. Siriwardena, W. Tempel, Z.-J. Liu, J. Glushka, B.-C. Wang, K. W. Moremen, Mechanism of Class 1 (glycosylhydrolase family 47) alpha-D-mannosidases involved in *N*-glycan processing and endoplasmic reticulum quality control, *J. Biol. Chem.,* 2005, *280*, 16197

Research Interests
Study of Carbohydrate Protein Interactions & Glycobiology
Synthetic Organic Chemistry

Honors and Awards
Visiting Professor, University of Hamburg, Germany (2009)
POWE Award (USA) (2004)
Forsyth-Grant-Hurford Fellowship, London University, (1982)
Joan Scoarse Fellowship (1982, London University)

Other Qualifications
Licentiate of the Royal Academy of Music, London, UK (1977)
Associate of the Royal College of Organists, London, UK 1979)
Fellow of the Trinity College of Organists, London, UK (1982)
Fellow of the London College of Music, London, UK (1980)

Aloysius Siriwardena & Le Laboratoire de Glycochimie, des Antimicrobiens et des Agroressources (LG2A) FRE 3517 CNRS), Amiens, France
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Dr Siriwardena is a senior research scientist of the Centre National de la Recherche Scientifique (CNRS) and visiting professor at the Technical University of Graz, Austria. He accepted his present position at the "LG2A" (FRE-3517-CNRS) in the middle of 2005. The "LG2A" is jointly supported by the "Université de Picardie Jules Verne" and the CNRS. It is composed of 26 permanent scientists. Since 2010, it has produced over 200 publications, 6 book chapters, 38 oral communications and 72 poster communications with 13 theses' submitted and 18 currently being pursued.

The "Laboratoire des Glucides" has become one the most important centers in France dedicated to research into carbohydrate-related problems. The specific areas of excellence include the chemistry and biochemistry of carbohydrates as well as the exploitation of sugar-derived biomass "waste" for useful purposes (green energy, cosmetics, etc., etc.). Amongst the central research themes of the Laboratoire des Glucides is the design and synthesis of natural compounds and/or analogs that serve as tools with which to modulate and study the roles of glycans in health and disease. Synthetic expertise includes the functionalization, purification and characterization of very polar compounds and includes the synthesis of complex oligosaccharides. The proven reputation of the Laboratoire both nationally and internationally continues to see its continued participation in many successful national and international consortia.

The central position of carbohydrates, glycans and glycobiology at the heart of Dr Siriwardena's research interests has seen him being implicated in several fruitful collaborative projects of an interdisciplinary nature with both French colleagues and others abroad. These include projects related to the study of viral entry, bacterial adhesion, cancer metastasis, Alzheimers and other neurodegenerative diseases, etc. This has seen support and funding not only from local sources (Picardie) but also from national (ANRS) as well as European (FP7 and COST projects) and international bodies (Franco-Indian, Franco-Pakistani, Franco-Austrian, etc.). This in turn has seen many postdocs from abroad working at the "Laboratoire", including researchers from countries including India, Pakistan Austria, China, the Ukraine, Spain, Portugal, Algeria, Tunisia and Morocco (and others). Collaborative projects with the US, Spain, Denmark, Ireland, the UK, Germany, Argentina, Canada are also ongoing.

The ambitious nature of many of the current and past projects in which Dr Siriwardena continues to be interested is also reflected in the number of highly cited publications he has co-authored as well as in the quality of the journals his work has appeared (JACS, Angewandte Chemie Int Ed., Nature Chemical Biology, Chemical Communications, Nanoscale, etc.) including 4 which have been highlighted since 2012. Acknowledgement of the esteem in which Dr Siriwardena's is held by the wider community is reflected in the number and variety of collaborative projects in which he is implicated and the numerous invitations he has and continues to receive to present his research both at home and abroad (including next years International Carbohydrate Symposium to be held in Bangalore).

The "Laboratoire des Glucides" is fully equipped for conducting organic synthesis (1600 m^2 of laboratory and office space). It also possesses all routine equipment for analysis and characterization of complex organic compounds. These include: Brucker DMX 300MHz DRX 500MHz and 600MHz NMR spectrometers and work stations; Waters electrospray and Waters QTOF Ultima mass spectrometers (MS) including low and high resolution capabilities (Dionex, preparative and analytical LC-MS., FTIR, etc. Since 1st January 2008, the laboratory is associated with the "Institut de Chimie Picardie", a "Fédération de Recherche" which includes the UMR6007 and 2 technical platforms which house the NMR and mass spectroscopic resources as well as a host of other analytical resources.

Selected Publications

A. Bericebar, C. Grandjean and A. Siriwardena, Synthesis & Biological Activity of Aminocyclitol Glycosidase Inhibitors: Mannostatins, Trehazolin, Allosamidins and their Analogues, *Chemical Reviews*, **1999**, *99*, 779

A. Siriwardena, M. R. Jorgensen, M. A. Wolfert, M. L. Vandenplas, J. N. Moore, G. J. Boons. Synthesis & Proinflammatory Effects of Peptidoglycan-Derived Neoglycopeptide Polymers, *J. Am. Chem. Soc.*, **2001**, *123*, 8145

E. Arranz-Plaza, A. S. Tracy, A. Siriwardena, J. M. Pierce, G.-J. Boons. High Avidity, Low Affinity Multivalent Interactions and the Block to Polyspermy in *X. Laevis. J. Am. Chem. Soc*. **2002**, *124*, 1305

A. H. Siriwardena, F. Tian, S. Noble, J. A. Prestegard. A Novel NMR-Based Method for Library Screening: Exploiting Competitive Binding to Rapidly Identify Active Ligands in Mixtures. *Angewandte Chemie International Edition*, **2002**, *41*, 3454

S. Thobhani, B. Ember, A. Siriwardena, G.-J. Boons. Multivalency and the Mode of Action of Bacterial Sialidases, *J. Am. Chem. Soc*. **2003**, *125*, 7154

J. Gonzalez-Outereirino, J. Glushka, A. Siriwardena, R J. Woods. The Structure and Conformational Behavior of Sulfonium Salt Glycosidase Inhibitors in Solution: A Quantum Mechanical-NMR Approach, *J. Am. Chem. Soc*., **2004**, *126*, 6866.

A. Siriwardena, S. El-Daher, G. Way, B. Winchester, H. Strachan, K. W. Moremen, G.-J. Boons. Potent and Selective Inhibition of Class II alpha-D-Mannosidase Activity by the Bicyclic Sulfonium Salt, *ChemBioChem.*, **2005**, *6*, 1.

K. Karaveg, A. Siriwardena, W. Tempel, Z.-J. Liu, J. Glushka, B.-C. Wang, K. W. Moremen, Mechanism of Class 1 (glycosylhydrolase family 47) alpha-D-mannosidases involved in *N*-glycan processing and endoplasmic reticulum quality control, *J. Biol. Chem.*, **2005**, *280*, 16197

Recent Publications

Y. Zhu, M. Suits, A. J. Thompson, S. Chavan, Z. Dinev, C. Dumon, N. Smith, K. Moremen, Y. Xiang, A. Siriwardena, S. Williams, H. Gilbert, G. J. Davies, The Expansion of a Calcium-Dependent Family of alpha-Mannosidases in a Human Gut Symbiot Reflects its Capacity to Utilize Host N-Glycans as an Important Nutrient, *Nature Chem. Biol.*, **2010**, 6, 125

S. Szunerits, J. Niedziolka-Jonsson, R. Bouherroub, P. Woisel, J.-S Baumann, A. Siriwardena, Label-free detection of lectins using carbohydrate-modified boron-doped-diamond interfaces, *Analytical Chemistry*, **2010**, 82, 8203

A. H. Siriwardena, A. Barras, F. A. Martin, O. Bande, J.-S. Baumann, J.-M. Ghigo, R. Boukherroub, C. Beloin, S. Szunerits, Could Nanodiamonds be a Girls Best Friend? *Glycoconjugate J.*, **2011**, 28, 216

A. J. Thompson, J. Dabin, J. Iglesias-Fernández, A. Ardèvol, Z. Dinev, S. J. Williams, A. Siriwardena, O. Bande, C. Moreland, T.-C. Hu, D. K. Smith, H. J. Gilbert, C. Rovira, G. J. Davies, The Reaction Coordinate of a Bacterial GH47 alpha-Mannosidase: a combined Quantum Mechanical & Structural Approach, *Angew. Chem. Int. Ed*, **2012**, 51, 10997 (highlighted article)

I. Kaminska, A. Barras, Y. Coffinier, W. Lisowski, S. Roy, J. Niedziolka-Jonsson, P. Woisel, J. Lyskawa, M. Opallo, A. Siriwardena, R. Boukherroub, S. Szunerits, Preparation of a Responsive Carbohydrate-Coated Biointerface Based on Graphene/Azido-terminated Tetrathiafulvalene Nanohybrid Material, *Applied Materials & Interfaces*, **2012**, 4, 5386 (highlighted article)

N. Maalouli, A. Barras, A. Siriwardena, B. Pinchemel, M. Bouazaoui, R. Boukherroub, S. Szunerits, Comparison of Photo- and Cu(I)-Catalyzed "Click" Chemistries for the Formation of Carbohydrate SPR Interfaces, *Analyst*, **2012**, DOI: 10.1039/C2AN36272D

A.-C. Gouget-Laemmel, J. Yang, M. A. Lodhi, A. Siriwardena, D. Aureau, R. Boukherroub, J.-N. Chazalviel, F. Ozanam, S. Szunerits, Functionalization of Azide-terminated Silicon Surfaces with Glycans using « click » chemistry: XPS and FT-IR Study, *J. Physical Chem C*, **2013**, 117(1), 368-375

M. Mazur, A. Barras, V. Kuncser, A. Galatanu, V. Zaitzev, P. Woisel, J. Lyskawa, W. Laure, A. Siriwardena, R. Boukherroub, S. Szunerits, Iron Oxide Magnetic Nanoparticles with Versatile Surface Functions Based on Dopamine Anchors, *Nanoscale*, **2013**, DOI: 10.1039/C3NR33506B (highlighted article)

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Siriwardena, K. K. Pulukuri, P. S. Kandiyal, S. Roy, O. Bande, S. Ghosh, J. M. Garcia Fernàndez, F. Ariel Martin, J.-M.Ghigo, C. Beloin, K. Ito, R. Woods, R. S. Ampapathi, T. K. Chakraborty, Sugar-Modified Foldamers as Conformationally Defined and Biologically Distinct Glycopeptide Mimics, *Angewandte Chemie. Int. Ed.*, ***2013***, *52*, 10221
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Zoidl, M.; Müller, B.; Torvisco, A.; Tysoe, C.; Benazza, M.; Siriwardena, A.; Withers, S. G.; Wrodnigg, T. M., Concise synthesis of C-1-cyano-iminosugars via a new Staudinger/aza Wittig/Strecker multicomponent reaction strategy, *Bioorg. Med. Chem. Letters*, **2014**, 24, 2777

Siriwardena, A.; Sonawane, D. P.; Bande, O. P.; Markad, P. R.; Yonekawa, S.; Tropak, M. B.; Ghosh, S.; Chopade, B. A.; Mahuran, D. J.; Dhavale, D. D. Synthesis of 1,5-Dideoxy-1,5-iminoribitol C-Glycosides through a Nitrone–Olefin Cycloaddition Domino Strategy: Identification of Pharmacological Chaperones of Mutant Human Lysosomal β-Galactosidase, *J. Org. Chem*., **2014,** 79, 4398

Khanal, M.; Barras, A.; Vausselin, T.; Feneant, L.; Boukherroub, R.; Siriwardena, A.; Dubuisson, J.; Szunerits, S., Boronic acid-modified lipid nanocapsules: a novel platform for the highly efficient inhibition of hepatitis C viral entry, *Nanoscale* **2015**, 7, 1392.

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Taouai, M.; Abidi, R.; Garcia, J.; Siriwardena, A.; Benazza, M., Synthesis of unsymmetrical thioethers using an uncommon base-triggered 1,5-thiol transfer reaction of 1-bromo-2-alkylthiolcarbonates, *J. Org. Chem.*, **2014**, 21, 10743.

Khanal, M.; Barras, A.; Vausselin, T.; Feneant, L.; Boukherroub, R.; Siriwardena, A.; Dubuisson, J.; Szunerits, S. Boronic acid-modified lipid nanocapsules: a novel platform for the highly efficient inhibition of hepatitis C viral entry, *Nanoscale,* **2015**, 7, 1392-1402.

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