COST Action CM1102

Multivalent Glycosystems for Nanoscience Conference

October 29-30, 2015

Antalya, Turkey

Meeting Information

Multivalent Glycosystems for Nanoscience CM1102

http://cost-cm1102.bangor.ac.uk/

Carbohydrates constitute the most abundant class of biomolecules on Earth. They have diverse biological roles ranging from energy storage to mediating interactions between living cells. Carbohydrates that are attached to proteins, lipids and synthetic multivalent scaffolds (i.e. glycoconjugates) can be used as anti-adhesive drugs against bacteria or viruses, or bioimaging agents that can target specific tissues. However, they can also have applications in materials science as nanoscale building blocks for hydrogels and templates for making nano-structured hard materials.

We aim to build a dynamic network across Europe focused on developing glycoconjugates for nanoscience applications. We develop new methods for producing nanomaterials for applications in drug delivery, in gene targeting and as diagnostic/prognostic tools. The conference will foster new collaborations to transform glycoconjugate research in Europe by establishing a new frontier at the interface with nanoscience.

Venue:

The Rixos Downtown Antalya Hotel http://downtownantalya.rixos.com/

Travel Information:

- Airport:
  Antalya International Airport (http://www.aytport.com/en/index_1.asp) has regular direct flights from several European cities. You may also connect through Istanbul.

- Airport to Hotel Limo service: Advance reservation is required.
  (https://www.securedrivetravel.com.tr/Reservation.aspx) The cost is 43 TL (about 15 EUR)

- Taxi from airport to hotel is around 20 EUR.

Accommodation:

- We negotiated at a special price with the hotel for the conference for 28-30 October.

  Single Room (1 person): 132 EUR/day
  Double Room (2 persons): 190 EUR/day

  These rates include all meals, conference rooms and gala dinner.

  If you need to reserve rooms for additional days (other than 28-30 Oct), you should contact the hotel for reservation from Mustafa.Akin@rixos.com and Dilay.Aydogan@rixos.com

  Please mention "COST Meeting – Bilkent Univ" in the payment forms, and bank money transfer information.

  You are recommended to use hotel facilities and the beach on wednesday (Oct 28) and saturday (Oct 30) because you will spend most of your thursday and friday for the meeting. The hotel has a private beach, and there is a shuttle running in front of the hotel.

Visa Information:

- You may obtain visa for entrance to Turkey through online or through local consulate.
  The e-Visa is an alternative to visas issued at Turkish missions and at the ports of entry.
  https://www.evisa.gov.tr/en/

Shopping and Dining:

- Walking distance to the hotel, there is a shopping center called Antalya Migros Shopping Center (http://www.antalyamigros.com/en/).

Social Excursion:

- Antalya is a famous touristic city. (https://en.wikipedia.org/wiki/Antalya)
- You can organize tours to visit historical sites from the hotel reservation desk.
- Antalya Museum is just next to the hotel. (http://www.antalyamuzesi.gov.tr/en)
- You can walk to old city and the historical Marina (Kaleici) from the Hotel. You should take a boat tour from the marina.
  Map:
  https://www.google.com/maps/dir/Rixos+Downtown,+Sak%C4%B1p+Sabanc%C4%B1+Blv+No:18,+Konyaalt%C4%B1+Sahili,+Konyaalt%C4%B1,+07050+Antalya/Kaleici+Yat+Limani,+Muratpa%C5%9Fa,+Tuzkap%C4%B1s%C4%B1+Sokak,+Antalya,+Turkey/@36.8842909,30.6842284,15z/data=!4m14!4m13!1m5!1m1!1s0x14c390344c1f1e6d:0xadbc12eed7aa5b79!2m2!1d30.669879!2d36.884632!1m5!1m1!1s0x14c39004fc9ddb65:0x4b1f80400f7f1bb7!2m2!1d30.703556!2d36.884281!3e2

- Antalya Aquarium, very close to the hotel, just a short taxi ride away.
  (http://www.antalyaaquarium.com/contact/map-location)

Attendance Sheet:

Please register and sign the attandence sheet for all days during the program.

Conference Program

THURSDAY (Oct 29)	
8:30–9:00	Registration
9:00 – 9:20	Welcome / Introductory Comments **Mustafa Guler, Bruce Turnbull** and **Cristina Nativi**
9:20–9:40	**Mustafa Guler**, *"Self-Assembled Glycopeptide Nanostructures"*, Bilkent University, Turkey.
9:40 –10:00	**Thisbe Lindhorst**, *"Organizing multivalency in carbohydrate recognition"*, Christiana Albertina University, Germany.
10:00-10:15	**Jose M. Garcia Fernandez**, *"Multivalent aminosugars as dual lectin and DNA binders"*, Institue of Chemical Research, Spain.
10:15– 10:35	**Lothar Elling**, *"Chemo-enzymatic synthesis of glycopolymer brushes and neo-glycoproteins for multivalent lectin recognition"*, RWTH Aachen University, Germany.
10:35 - 11:00	**Coffee Break**
11:00 – 11:15	**Roland Pieters**, *"Multivalent inhibition ob bacteria and bacterial toxins"*, Utrecht University, Netherlands.
11:15 - 11:30	**Giulio Goti**, *"Scaffold optimisation and activity evaluation of tetra-pseudoglycosylated MBL antagonists"*, UniversitàdegliStudi di Milano, Italy.
11:30 - 11:45	**RekoLeino**, *"From mannose to small amphiphilicpolyol - perfect linearity leads to spontaneous aggregation"*, ÅboAkademi University, Finland.
11:45 - 12:00	**Melis Sardan**, *"Multivalent GlycopeptideNanosystemsfor Enhanced Lectin Binding"*, Bilkent University, Turkey.
12:00 - 12:15	**Serge Perez**, *"Building, Seeing and Playing with Complex Carbohydrates"*, Grenoble University, France.
12:15 - 12:30	**João Pais**, *"Insights into the mechanism of action of antibacterial surfactants"*, Universidade de Lisboa, Portugal.
12:30 - 14:00	**Lunch**
14:00 - 14:20	**Matthew Gibson**, *"Multiplexed Multivalent GlycoSensors"*, University of Warwick, UK.
14:20-14:35	**Sarah-Jane Richards**, *"Glycosylated gold nanoparticle biosensors: Label-free and high-throughput evaluation of glycan/lectin interactions"*, The University of Warwick, UK.
14:35 - 14:55	**Amelia Rauter**, *"Foods for the brain - a new perspective"*, University of Lisbon, Portugal.
14:55 - 15:10	**Vanessa Porkolab**, *"Designing nanomolar antagonists of DC-SIGN-mediated HIV infection: Improvement of the multivalency presentation"*, Université Joseph Fourier, FR.

15:10 - 15:30	**David Fulton**, *"Polymer-Scaffolded Dynamic Combinatorial Libraries: A conceptually newapproach to the design of multivalent glycopolymers"*, Newcastle University, UK.
15:30 - 16:00	**Coffee Break**
16:00 - 16:15	**Cristina Vicent**, *"Carbohydrate-DNA interaction"*, IQOG-CSIC, Spain.
16:15 - 16:30	**Andrea Taladriz-Sender**, *"Cationic glico-oligoamides in DNA molecular recognition"*, CSIC/IQOG, Spain.
17:00- 19:00	**CM1102 MC Meeting**
19:00	**Dinner**
FRIDAY (Oct 30)	
9:00 – 9:20	**Bruce Turnbull**, "*Engineering bacterial toxins for use as inhibitors and delivery vehicles* ", University of Leeds, UK.
9:20-9:35	**Vladimir Kren**, *"Modified multivalent poly-N-acetyllactosamineglycans as novel ligands of human galectin-3"*, Institute of Microbiology, Czech Republic.
9:35 – 9:55	**Han Zuilhof**, *"Sweet surfaces"*, Wageningen University, Netherlands.
9:55–10:10	**Caroline Biggs**, *"Smart microarray platforms for understanding biochemical interactions"*, The University of Warwick, UK.
10:10 – 10:30	**Clare Mahon**, *"Dynamic polymer systems capable of lectin recognition"*, University of Leeds, UK.
10:30 - 11:00	**Coffee Break**
11:00 – 11:15	**Jean-Louis Reymond**, *"Glycopeptidedendrimer biofilm inhibitors"*, University of Bern, Switzerland.
11:15 - 11:30	**João Ribeiro**, *"Engineering and Structural Characterization of a Novel, Specific Sialic Acid-Binding Protein"*, CERMAV-CNRS, France.
11:30 - 11:45	**BeritSmestad Paulsen**, *"Bioactive polysaccharides from Malian medicinal plants"*, University of Oslo, Norway.
11:45 - 12:00	**Wolf-Dieter Fessner**, *"Multivalent Glyco-Nanoclusters of Cubic Symmetry by Thermal Click Chemistry"*, TechnischeUniversitaet Darmstadt, Germany.
12:00 - 12:15	**Diogo Vila-Viçosa**, *"Antibacterial sugar-based surfactants targeting lipid bilayers: mechanistic insights from molecular dynamics simulations",* Universidade de Lisboa, Portugal.

12:15 - 12:30	**Juan M Benito**, *"Harmonized tuning of nucleic acid and lectin binding properties with multivalent cyclodextrins for macrophage-selective gene delivery"*, Universidad de Sevilla, Spain.
12:30 - 14:00	**Lunch**
14:00 - 14:20	**Seunghwan Lee**, *"Lubricity of mucins as boosted by mucoadhesion"*, Technical University of Denmark, Denmark.
14:20-14:35	**Diego Garcia-Puentes**, *"Chemical tools to study carbohydrate-DNA minor groove interactions"*, Instituto de QuimicaOrganica General, Spain.
14:35 - 14:55	**Aloysius Siriwardena**, *"Sugars Shapes & Peptide Folds: Synthetic Sugar Mimetics that Modulate Protein Function"*, CNRS, France.
14:55 - 15:10	**Sinclair Sweeney**, *"Synthesis of trimeric coiled coils presenting lactose as glycoclusters"*, National University of Ireland Galway, Ireland.
15:10 - 15:30	**Olivier Renaudet**, *"Multivalent glycocyclopeptides: synthesis and applications"*, University of Grenoble, France.
15:30 - 16:00	**Coffee Break**
16:00 - 16:20	**David Benito**, *"Fluorescent Multivalent Glycan Probes for Glycobiology Research"*, University of Bristol, UK.
16:20 - 16:35	**Ozum Sehnaz Gunel**, *"Glycopeptidenanofibers for chondrogenic differentiation"*, Bilkent University, Turkey.
16:35 - 16:55	**Anne Imberty**,*"Multivalent lectins and cell surfaces: labeling and dynamics"*, CNRS, France
16:55- 17:00	**Bruce Turnbull** Closing remarks
19:00	**Gala Dinner**

Oral Presentations

Mustafa O. Guler
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Self-Assembled Glycopeptide Nanostructures

Design and synhtesis of glycopeptides for building self-assembled nanostructures will be discussed. These nanostructures can interact with receptors related to glycobiology. These nanostructures have ability to mimic extracellular matrix materials and they can be utilized for regenerative medicine applications.

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Organizing multivalency in carbohydrate recognition

Multivalency of molecular interactions is a fundamental principle in carbohydrate recognition. It influences the avidity and specificity of carbohydrate-protein interactions as well as it enables supramolecular changes on the cell surface that are essential for cell-cell communication. During the last two decades it has become clear that there is not one mechanism underlying multivalency effects in glycobiology, but that there are a multitude of biological processes involving multivalency in one or the other way. These processes allow to control, regulate and fine-tune the complex life of eukaryotes. In this account, synthetic multivalent glyco-assemblies will be presented in order to “organize” multivalency. This approach is based on the idea that changes of ligand orientation as well as changes of their conformational availability are regulating parameters in carbohydrate recognition, in particular on the cell surface. Examples will include molecular dynamics of glycodendrimers, photoswitchable glycoazobenzene-SAMs to switch cell adhesion, and carbohydrate-scaffolded divalent glycothymine derivatives that can be intramolecularily dimerized by [2+2] photocycloaddition.

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Multivalent aminosugars as dual lectin and DNA binders

The incorporation of carbohydrate functional elements in the architecture of polycationic amphiphilic cyclodextrins (paCDs) provides glycosylated paCDs (pGaCDs) that form transfectious nanocomplexes (glycoCDplexes) with pDNA. In this study, we aimed at elucidating the internalization mechanisms at play and their incidence in transfection efficiency for glycoCDplexes formulated with 6-amino-6-deoxy-b-Dglucopyranosyl-appended pGaCDs in comparison with mannosylated and non-glycosylated congeners. Preliminary data showed a relatively high uptake of the 6-aminoglucosylated nanocomplexes by BNLCL2 hepatocytes that correlated with a strong affinity towards the galactose-specific peanut agglutinin (PNA) lectin, suggesting that the galactose-binding asialoglycoprotein receptor at the surface of hepatocytes might be involved in glycoCDplex internalization. Transfection kinetics, internalization rates and protein expression data in BNL-CL2 ASGPR-expressing cells and COS-7 ASGPR-devoid epithelial cells in the absence and presence of different inhibitors of clathrin-dependent (chlorpromazine), caveolae-dependent (genistein) and macropinocytosis (amiloride) endocytic routes evidenced significant differences in cell uptake pathways and fate of glycoCDplexes as compared with CDplexes. Most importantly, such differences were dependent on the cell type and on the carbohydrate coating moiety. Clathrin-mediated uptake in BNLCL-2 cells is particularly favored for the 6-amino-6-deoxyglucose CDplexes, supporting the interplay of specific recognition phenomena. Competitive uptake and transfection experiments conducted in the presence of asialofetuin or of a polyclonal ASGPR-antibody, as well as siRNA-mediated ASGPR-specific gene knockdown, supported the involvement of ASGPR, firmly demonstrating the dual role of the 6-amino-6-deoxyglucose motif as DNA and lectin receptor ligand. The results reinforce the use of carbohydrates in glycoCDplexes to modulate cellular uptake and transfection capabilities in a cell-dependent manner.

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Chemo-enzymatic synthesis of glycopolymer brushes and neo-glycoproteins for multivalent lectin recognition

We have developed a toolbox of glycan synthesizing and modifying enzymes including glycosidases, glycosynthases, and Leloir-glycosyltransferases for the regio- and stereoselective synthesis of glycoconjugates. Our on-going work focuses on native and modified glycoconjugates in a novel concept of a Glyco-BioInterface by bio-functionalization of biomaterial surfaces and formation of multivalent scaffolds. We here present the chemo-enzymatic synthesis of glycopolymer brushes as a novel platform for lectin recognition. Controlled polymer growth on silicon substrates is combined with the synthesis of N-acetyllactosamine (LacNAc) oligomers (di- to hexasaccharide) by glycosyltransferases (β4GalT, β3GlcNAcT) directly on the polymer brushes. With these glycopolymer brushes on biosensor surfaces lectin binding is monitored by electrochemical impedance spectroscopy (EIS) and localized surface plasmon resonance (LSPR). In all setups, binding of the lectins GSII, ECL, and the receptor domain of toxin A from C. difficile is highly selective and reveals binding to the specific glycan epitope in the nanomolar range. In the second example, the β4GalTY284L mutant, β3GlcNAcT, β4GalT, and β3GlcNAcT are used for the synthesis of LacNAc and N,N-diacetylactosamine (LacDiNAc) terminated LacNAc oligomers. Conjugation to bovine serum albumin (BSA) yields a series of multivalent neo-glycoproteins showing high selectivity for binding of tumor-associated human galectin-3 to the LacDiNAc epitope. Multivalent binding effects are observed with increasing numbers of attached glycan reaching binding and inhibition constants in the nanomolar range. The presented multivalent scaffolds have potential for biomedical applications.

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Multivalent inhibition ob bacteria and bacterial toxins

Recent progress in the detection of cholera toxin inhibition will be discussed. New spacer development and their evaluation in the inhibition of LecA. Multivalent Streptococcus suis inhibition will also be discussed, with possible addition of other recent findings.

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Scaffold optimisation and activity evaluation of tetra-pseudoglycosylated MBL antagonists

Mannose Binding Lectin (MBL) is a circulating multimeric calcium dependent (C-lectin) protein that acts as a first-line host defence by selectively recognizing and binding to polyglycosylated surfaces of invading pathogens or damaged self cells.[1]MBL is also able to modulate inflammation and it is likely involved in reperfusion damage in acute stroke,[2] therefore representing an attractive target for the development of new drugs against this disease. Our groups have already reported that pseudoglycosylated tetravalent dendrimers based on polyester scaffolds are good antagonists of MBL, with kd values in the low micromolar range. They were shown to supply a protective effect in a mouse model of brain stroke, reducing the reperfusion damage with a surprisingly wide therapeutic window.[3] Unfortunately, these constructs proved to be rather chemically unstable: the polyester scaffold does not survive silica gel chromatography in either direct or reverse phase and slowly hydrolyses in water solution at physiological pH (27% hydrolysis in 6h). Here we present the synthesis of new dendrimers characterised by a stabilised version of the scaffold that allows to obtain still water soluble compounds with a grater chemical stability. Results of in vitro SPR binding assays of the new dendrimers to MBL will also be discussed.

1) Weis, W. I.; Drickamer, K.; Hendrickson, W. A. Nature 1992, 360, 127-134.
2) Osthoff, M.; Katan, M.; Fluri, F. et al. PLoS One 2011, 6, e21338.
3) Orsini, F.; Villa, P.; Parrella, S. et al. Circulation 2012, 126, 1484-1494.

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From mannose to small amphiphilic polyol - perfect linearity leads to spontaneous aggregation

Terminally unsaturated and diastereomerically pure polyol derived from D-mannose shows spontaneous aggregation behavior in water solution. In order to study and clarify this unforeseen phenomenon, a conformational study based on NMR spectroscopy combined with ab initio geometry optimizations using the COSMO-solvation model was pursued. The results, together with X-ray diffraction studies, suggest a low energy linear conformation for this particular substrate both in crystalline and aggregated states and in solution. For such small-sized acyclic carbohydrate derivatives, the linear conformation appears to be a key prerequisite for the unusual molecular self-assembly reported herein.

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Designing Multivalent Amphiphilic Glycopeptide Systems having Enhanced Lectin Binding Affinity

Carbohydrates, which exist on the surface of cell membrane, take part in many different cellular processes such as growth, motility, morphology, differentiation. All these processes are controlled by extracellular signals; thus, this sugar moieties attached onto the cell surface have also important role in cellular recognition, inflammation, signal transduction and infection of pathogens. To improve the recognition ability of sugar units by cells, the presentation of the sugar on the structure is very critical. The interaction of multivalent presentations can give rise to the formation of numerous simultaneous complexation events that affords both high observed affinity and high functional affinity. Lectins are beneficial tools to study the effect of multivalency in protein-carbohydrate binding systems. This sugar binding proteins are a class of proteins found in all biological systems ranging from viruses and bacteria to plants and animals. In this kind of interactions, the position of the carbohydrate on the polymer backbone or any other entity is very essential to obtain collective binding; i.e., glycocluster effect. In this study, two different sugar units (mannose, lactose) were used to incorporate into the peptide backbone. Their chemical structures were idetified by LC-MS and puried with prep-HPLC. Also, the secondary structures and morphological characterization were performed by CD and TEM, respectively. To investigate multivalent effect of glycopeptide structures, Concanavalin A and peanut agglutinin (PNA) were selected as recognition elements for mannose and lactose, respectively.

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Building, Seeing and Playing with Complex Carbohydrates

One of the challenges facing Glycoscience is the development and implementation of robust and validated informatics toolbox enabling accurate and fast determination of complex carbohydrate sequences extendable to 3D prediction, computational modeling, data mining and profiling. The concomitant expansion of stable and integrated databases, cross-referenced with popular bioinformatics resources should contribute to connecting glycomics with other –omics. Glycoscience benefits from repositories that store and disseminate data to the scientific community, catering mostly to the area of carbohydrate chemistry. Because of their inherent complexity and variability, data bases dealing with the 3D structural features of complex carbohydrate containing molecules still lag behind. This may be quite detrimental to the development and construction of complex molecular assemblies where carbohydrates display their unique functionalities Glyco3D (1) features a family of databases covering the 3D features of mono-, di-, oligo-, poly-, saccharides, glycosyltransferases, lectins, monoclonal antibodies and glycosaminoglycan-binding proteins. This ensemble offers a unique opportunity to characterize the 3D features that a given oligosaccharide can assume in different environments. A common nomenclature has been adopted that conforms to the recommendations for carbohydrates and including the constraints required by the developing field of glycobiology in terms of visualization and encoding. A search engine has been developed that scans the full content of all the data bases for queries related to sequential information of the carbohydrates or other related descriptors. Whereas macromolecular builders are also made available for generating three-dimensional structures of polysaccharides and complex carbohydrates, there was a clear need to develop a molecular visualization program that would cope with the uniqueness of the range of carbohydrate structural features, either alone or in complex environments in particular with proteins and lipids. To this aim, a video game-based computer graphic software (SweetUnityMol (2)) was developed. All the specific structural features displayed by the simplest to the most complex carbohydrate-containing molecules have been taken into account and can be conveniently depicted. This concerns the identification of monosaccharides types, conformations, location in single chain or multiple branched chains, depiction of secondary structural elements and the essential constituting elements in very complex structures. In all these instances, particular attention was given to cope with the accepted nomenclature and pictorial representation used in carbohydrate chemistry, biochemistry and glycobiology. This program closely follows the most accepted symbolic representations for monosaccharides and existing formats for atomic coordinates and opens the route to pictorial representation of carbohydrates when studied at the “coarse-grain” level.

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Insights into the mechanism of action of antibacterial surfactants

Will be presented studies on the mechanism of action of the dodecyl 2,6-dideoxy-α-L-arabino-hexopyranoside which exhibits antibacterial properties against Bacillus species . Its impact on bacterial vitality and viability, metabolic reconstruction using phenotypic microarrays (Biolog®) and a genetic approach was carried out by testing multiple mutant libraries, such as random transposition and specific knock-out of several membrane related targets, using as a model strain B. cereus ATCC 14579. The results obtained suggest that this antibacterial does not act on a specific molecular target, but most likely on a cellular structure, like the cellular membrane. In order to verify or disprove this theory, the effects of the compound in the bacterial sporulation cycle and in different cellular structures were assessed, using protoplasts and spheroplasts as well as imaging techniques, namely atomic force microscopy and fluorescence microscopy. A summary of the results obtained and our conclusions regarding the mechanism of action will be presented and discussed.

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Multiplexed Multivalent GlycoSensors

The use of glycans in diagnostics (especially to detect lectins) is limited by their low affinity and low specificity - any given glycan can bind multiple lectins, thus giving rise to false positives. Here we make use of multivalent surfaces and particles to overcome the affinity problem via the cluster glycoside effect. Secondly, we use multiplexed sensors to generate unique 'pattens' of lectin (or micro-organism) binding to carbohydrates to generate a barcode - using simple mathematical algorithms it is possible to distinguish between (mixtures) of lectins, even those with similar specificity. Conjugation to gold nanoparticles enables this to be used as a 'label' free biosensor.

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Glycosylated gold nanoparticle biosensors: Label-free and high-throughput evaluation of glycan/lectin interactions

The development of new analytical tools to probe pathogenic infection processes and as point-of care diagnostics is crucial to combat the spread of infectious diseases or to detect biological warfare agents. There is a great need for biosensors that are fast, label-free, sensitive and inexpensive. Glycosylated gold nanoparticles that change colour due to lectin-mediated aggregation may find wide applicability as biosensors of bacteria and toxins. Here we present the use of precision polymer coated gold nanoparticles to negotiate the delicate balance between saline stability and the speed of the colorimetric readout.[1] These simple, monosaccharide conjugated gold nanoparticles are powerful tools for probing protein-carbohydrate interactions. Using a multiplexed assay and linear discriminant analysis differentiation between lectins and toxins such as Ricin or the cholera toxin[1] and bacterial phenotypes[2] is demonstrated. We have shown that the colour change in response to the correct glycan-lectin pairing can be determined not only spectrophotometrically but by using the simple combination of a mobile phone camera and image analysis freeware, providing an ultra-low cost route to biosensors.[3]

1. S.-J. Richards and M. I. Gibson, ACS Macro Lett., 2014, 3, 1004.
2. S.-J. Richards, E. Fullam, G. S. Besra and M. I. Gibson, J. Mater. Chem. B, 2014, 2, 1490
3. L. Otten, S.-J. Richards, E. Fullam, G. S. Besra and M. I. Gibson, J. Mater. Chem. B, 2013, 1, 2665"

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Foods for the brain - a new perspective

It is widely accepted that there is great potential to use dietary advice/interventions to delay onset, ameliorate or slow down decline in individuals either at risk, or already displaying symptoms of, many chronic health conditions, including metabolic, oncogenic and cognitive disorders. In this presentation we will highlight new perspectives for the prevention of Alzheimer's disease by interventions at the molecular level.

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Designing nanomolar antagonists of DC-SIGN-mediated HIV infection: Improvement of the multivalency presentation

The most common way for HIV (Human Immunodeficient virus) infection is through sexual transmission across genital mucosa. In mucosal tissues, dendritic cell subsets transmit HIV to T cells through C-type lectins. Dendritic cell subsets can be distinguished by their expression of C-type lectins: Langerhans cells (LCs) specifically express Langerin and dermal dendritic cells (DDCs) express DC-SIGN. LCs reside in mucosal epithelia, such as the ectocervix, vagina and foreskin, whereas DC-SIGN+ DDCs reside in the sub-epithelium. Thus, Langerin Cells are the first Dendritic cells subset to encounter HIV. DC-SIGN, a C-type lectin receptor, plays a role in virus transfer to T cells (“in trans” infection), and notably via de novo infection of DCs itself (“cis ” infection). In contrast to DC-SIGN, Langerin prevents HIV-1 transmission by LCs. HIV captured by Langerin was internalized into Birbeck granules and degraded. Indeed, Langerin is considered as a natural barrier to HIV. Langerin and DC-SIGN have common carbohydrate specificities; they both interact with mannose and fucose structures. However, DC-SIGN, largely dependent on high-mannose-content moieties, permits to bind HIV envelope, gp120. The multivalent attachment mode between gp120 and DC-SIGN, results in interaction of high affinity. It's necessary to develop inhibition strategies with mimic multivalency and based on mannose or fucose-based ligands. In other words, any strategy aiming to block DC-SIGN should avoid to block langerin. However, both lectin have common specificity towards oligosaccharides making this goal challenging. The Bernardi and Fieschi groups have been collaborating on a project directed towards the discovery of selective multivalent ligands of DC-SIGN based on the polyvalent presentation of monovalent glycomimetic molecules. The type of multivalent scaffolds is critical in the glycomimic presentation to optimize the avidity phenomenon between ligands and DC-SIGN. These molecules are characterized, in terms of relative affinity and avidity by surface plasmon resonance (SPR). Recently, a new compound with a rigid core is able to bind two actives sites of tetrameric DC SIGN, by chelate effect, allowing to reach, for the first time, a nanomolar activity for glycomimic-based derivatives.

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Polymer-Scaffolded Dynamic Combinatorial Libraries: A conceptually Approach to the Design of Multivalent Glycopolymers

At Newcastle we have developed the so-called Polymer-Scaffolded Dynamic Combinatorial Library (PS-DCL) concept as a method for the discovery of macromolecular ligands. PS-DCLs are constructed in aqueous solution by the grafting of functionalized residues onto a pre-formed polymer scaffold through dynamic hydrazone bonds, where the reversibility of these bonds allows residues to exchange and reshuffle their positions upon the polymer scaffold. The addition of macromolecular templates to PS-DCLs induces significant constitutional reorganization, with polymer chains selecting those residues, which promote strong binding and discarding those which do not. In this talk we demonstrate that a glyco-PS-DCL can respond to lectin templates (Concanavilin A or Heat Labile Toxin), re-equilibriating to preferentially incorporate the 'favoured' carbohydrate residue upon the polymer scaffold. By using solid-supported lectins, we isolated the 'best-binding' library members and show that they possess enhanced binding affinities with their lectin targets. These results indicate strongly that the PS-DCL concept is a viable route to discover glycopolymer inhibitors of carbohydrate binding proteins.

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Carbohydrate-DNA interaction

Considering that DNA lacks a structurally well-defined binding site, the establishment of the molecular basis for selective binding of active ligands to DNA grooves is challenging. Our strategy consists in finding strong and directional intramolecular hydrogen bonding motifs that could survive in aqueous solution and behave as efficient donor or acceptor moieties in the corresponding molecular recognition process. In this way, glyco-oligoamides, which are DNA minor groove binders, have been designed by modifying the basic oligoamide vector structure -Py-γ-Py-Ind (which is selective to bind a fixed DNA sequence) in its C-terminal end by introducing mannose and talose sugar moieties. These two sugars have been chosen, since they should present a directional intramolecular hydrogen bond between the amide NH at the anomeric position, and the sugar OH-2. Additionally, β-D-Tal could also establish one between OH-2 and OH-4. The characterization of these ligands has been performed by means of NMR and computational methods for both the free and bound state (to the Dickerson dodecamer and a 12-mer PolyAT-DNA). The existence of a directional intramolecular hydrogen bond between NH-5 and OH-2 of β-D-Man and NH-5, OH-2 and OH-4 of β-D-Tal in aqueous media has been demonstrated, showing that OH-2 of β-D-Man, and OH-4 of β-D-Tal, may act as cooperative hydrogen bonding donor centers for molecular recognition processes. Moreover, the possible influence of CH-π interactions on the establishment of intramolecular HBs has been also studied by computational methods

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Cationic glico-oligoamides in DNA molecular recognition

The study of basic atomic features of carbohydrate recognition interactions is a topic of current interest. Carbohydrate-DNA recognition is an interesting field due to the importance of such an interaction in biological systems. Carbohydrates are present in many antibiotics and anticancer drugs that target DNA and, in some cases, sugar residue is responsible for the sequences selectivity of the drug. However, the lack of knowledge on basic aspects of the interactions at the origin of selectivity and specificity of carbohydrate-nucleic acid binding makes it difficult to effectively design new carbohydrate-nucleic acid binders. To fill such knowledge gap, in previous studies we have applied a strategy based on the design of a neutral vector molecule (Ind-Py-γ-Py-sugar) which is able to bring structurally simple carbohydrates close to a particular DNA sequence. Nevertheless, in order to improve the solubility of these molecules in aqueous solution, stability of the complexes formed with DNA as well as their sequence selectivity towards different base pairs, a new vector has been designed, which displays a cationic moiety. The new vector exhibits a (R)-3,4-diaminobutyric acid, therefore resulting in the inclusion of an amine residue at the γ-turn. Furthermore, carbohydrates with cooperative hydrogen bonding centers (D-mannose and L-mannose) were introduced as monosaccharide unit, to study the influence of hydrogen bond cooperativity and chirality in DNA recognition process. A wide set of NMR-based binding and structural studies have revealed that the cationic ligand is significantly more efficient as DNA minor groove binder than its neutral parent analogue. Moreover, evidence of solubility enhancement has been found. Interestingly, a combination of supramolecular forces, hydrogen bonding and CH-π interactions, are involved in the definition of cationic glyco-oligoamides hairpin conformation. NMR and computational studies of the free ligand suggest, that not only is the intramolecular hydrogen bond present in aqueous media, but also CH-π interactions were at the origin of carbohydrate face selection towards the indole ring in the hairpin structure. Besides, biophysical interaction studies of the cationic glyco-oligoamides were performed (NMR, CD and ITC) with two sequences of DNA polymers (Poly(dA-dT)2 and Poly(dG-dC)2). Different behavior of D-mannose and L-mannose derivatives were observed, indicating that carbohydrate has a crucial role modulating structural and binding properties of cationic glico-oligoamides.

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Engineering bacterial toxins for use as inhibitors and delivery vehicles

Protein-carbohydrate interactions mediate many biological processes from adhesion of a sperm and egg that leads to life, to invasion of viruses, bacteria and their toxins that lead to diseases and sometimes death. In this lecture I will introduce a family of carbohydrate-binding proteins that are the toxins responsible for cholera and other diarrhoeal diseases. The bacterial toxins enter cells lining the intestine by first sticking to sugars at the cell surface. Following endocytosis, the toxins undergo retrograde transport through the Golgi and endoplasmic reticulum, from where the toxin can be released into the cytoplasm. I will describe how we are using a combination of synthetic chemistry, protein engineering and biophysical methods to re-engineer these toxins for use as multivalent anti-adhesive agents and as new drug delivery agents.

Relevant publications:

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Modified multivalent poly-N-acetyllactosamine glycans as novel ligands of human galectin-3

Carbohydrates are now recognized as important information transmitters in cellular processes. For physiological applications of carbohydrates the multivalency, which is dictated by the fact of rather weak carbohydrate-protein interactions, is to be addressed. This project aims at the synthesis of novel modified poly-LacNAc glycans and their evaluation as multivalent ligands of human Gal-3 lectin. A synthetic strategy will be developed to generate a library of branched and modified multivalent poly-LacNAc glycans. Additional modifications of terminal type 2 LacNAc units (Galβ4GlcNAc) by type 1 LacNAc (Galβ3GlcNAc), LacDiNAc (GalNAcβ4GlcNAc) epitopes as well as Gal-bound biotin moieties will be introduced to enhance the selectivity of the multivalent poly-LacNAc scaffold for Gal-3.

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Sweet Surfaces

We will outline the synthesis, surface attachment, characterization and diagnostic use of a series of sugar-coated surfaces for the capture of antibodies and bacteria. In addition, we will present the use of ambient mass spectrometry to characterize tailor-made surfaces, and show to which detail one can add MS to the tools of structural surface characterization.

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Smart microarray platforms for understanding biochemical interactions

Due to the global decrease in new antibiotic discovery and the increase in antibiotic resistance, there is an urgent need for new technologies to detect and probe bacterial infection. Carbohydrate arrays (glycoarrays) have proven highly effective in these processes.[1] These arrays are important research tools in studying infection, probing the mechanisms of bacterial, viral and toxin adhesion and in the development of new treatments for such infections.[2] At the start of the infection process, for example by cholera toxin, HIV or E. coli, pathogens adhere onto the host cells, commonly through protein-carbohydrate interactions. Probing these interactions can be efficiently achieved by the presentation of carbohydrates in a array format, which can detect bacteria and provide structural information on their adhesion proteins and carbohydrate specificities.[3] Current glycoarrays involve the immobilisation of carbohydrates onto glass slides, followed by the addition of fluorescent-labelled proteins to assess binding.[1] It would be preferable to interrogate whole bacteria, but this increases non-specific binding to the surfaces, reducing resolution and giving rise to false positive diagnoses. We have developed new and versatile methodologies to functionalise glass and silicon substrates with carbohydrates,[4] glycopolymers and switchable non-fouling polymers using 'click' type reactions. The use of switchable (thermoresponsive) polymers allows us to have a hydrophilic surface for resisting non-specific interactions, but also create high density arrays,[5,6] which have been characterised by ellipsometry, quartz crystal microbalance with dissipation, drop shape analysis and X-ray photoelectron spectroscopy. The arrays are as simple as self-assembling on gold, but with the cost saving of working on glass and silicon, and utilise covalently bound carbohydrates.

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Dynamic polymer systems capable of lectin recognition

"Synthetic materials with the capacity to adapt their properties in response to stimuli present the opportunity to deliver truly 'intelligent' materials, offering exciting new opportunities in biomedical and materials sciences. The expansion of the scope of such responsive materials will, however, require the synergistic exploitation of various supramolecular concepts. During this talk I will demonstrate that the combination of molecular recognition processes and dynamic covalent chemistry can be used to produce materials with unique adaptive properties, and that the stimuli-responsive characteristics of a material may be exploited to promote or prevent molecular recognition. Polymer-Scaffolded Dynamic Combinatorial Libraries (PS-DCLs)1-3 have been demonstrated to present a viable approach to the generation of macromolecular receptors for synthetic polymers and proteins. Carbohydrate-functionalised PS-DCLs4 have been prepared by the reversible conjugation of carbohydrates possessing acylhydrazide functionalities in their aglycone units onto aldehyde-functionalised polymer scaffolds. These systems have been shown to adapt their composition upon exposure to lectin templates, preferentially incorporating carbohydrates which bind selectively to the lectin added. This process generates polymers of significantly enhanced affinity for the template added, with enhancements in free energy of binding in the range of 5.2-8.8 kJ mol-1. Experiments indicate that these enhancements are not only as a consequence of increased display of the preferred carbohydrate residues upon polymer scaffolds, but that templation also rearranges key residues into strategic positions in order to interact more strongly with the template. This recognition-induced self-reorganisation presents a conceptually new approach to the design of macromolecular receptors for lectins. Dynamic Single-Chain Polymer Nanoparticles (SCPNs) decorated with carbohydrate units have also been produced, and have been shown to bind to complementary lectins. These molecular recognition processes may be exploited to drive the concentration of SCPNs onto lectin-functionalised surfaces, which in synergy with dynamic covalent bonds, allows the reorganisation of SCPNs into intermolecularly crosslinked polymeric films. Thermoresponsive polymers and SCPNs decorated with carbohydrate units have also been developed as on/off-switchable receptors for lectins. Below a critical temperature known as the lower critical solution temperature (LCST) these polymers exist as hydrated coils, and recognise lectins with association constants in the range of 105 – 106 M-1. When temperature is increased above the LCST, polymers are reversibly desolvated and collapse to yield hydrophobic globules, 'switching off' their ability to recognise lectins.

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Glycopeptide dendrimer biofilm inhibitors

Starting with fucosylated and galactosylated tetravalent glycopeptide dendrimers showing striking biofilm inhibition and dispersion effects on P. aeruginosa biofilms, a broad structure-activity relationship study based on sequence variations and structural investigations has allowed a refined understanding of the system, and the discovery of synergistic effects between different biofilm control agents.

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Engineering and Structural Characterization of a Novel, Specific Sialic Acid-Binding Protein

The binding of glycans to proteins is the primary way in which the information contained in those glycan structures is recognized, decoded, and lead to a biological effect. Sialic acids (SIAs) are critical components of the glycan epitopes that are recognized by microbial and animal SIA-binding lectins (or modules). The cell-surface glycocalyx of most mammalian cells is amply decorated with glycoconjugates that contain SIAs. Cases where changes are seen in glycan expression levels, or truncated as well as new epitopes are present, are usually related with malignancy such as cancer. Proteins are widely used as probes in glycoprofiling because of their specificity, which enables them to discriminate between a variety of structures. Sialylation profiling is particularly important in biopharma since it may influence both safety and efficacy of therapeutic glycoproteins. We have engineered and characterized a new SIA-binder, a member of the family 40 of the carbohydrate binding modules (CBM), originally encoded by gram-positive Clostridium perfringens nanI. A dimeric version of this CBM was also engineered to follow a lectin-like behavior and avidity effects. We herein present a complete multidisciplinary approach involving hemagglutination (HA), thermal shift assays (TSA), isothermal microcalorimetry (ITC), surface plasmon resonance (SPR), glycan arrays (GA) and x-ray crystallography (XR) to provide a full characterization of this novel, highly specific α2-3 sialic acid binder.

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Bioactive polysaccharides from Malian medicinal plants

Medicinal plants are a major source of drugs in most developing countries. In Mali the waterextracts of several plants are used for the treatment of malria, as well as against gastric ulcer and several othe ailments. The waterextracts are Rich in polysaccharides and studies we have performed over the last two decades have shown that these polysaccharides often have immunomodulating properties. The polysaccharides are often of pectic type, and our studies have given the basic structures of these, and results have also provided information about structure and activity relations. This will be presneted in the talk.

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Multivalent Glyco-Nanoclusters of Cubic Symmetry by Thermal Click Chemistry

We have developed efficient protocols for the synthesis of glycosylated acetylenedicarboxamides that by way of thermal alkyne-azide cycloaddition ("Click Chemistry") allow the rapid synthesis of glyco nanoclusters offering a designed 3D-multivalency of varying symmetry and varying degree of glycosylation. Ultimately, decoration of the hybrid cube-octameric silsesquioxane (COSS) scaffold leads to glycol-COSS nanocubes that display up to sixteen glycoside units within a highly uniform spherical environment for studies of biological recognition and potential multivalent cluster effects.

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Antibacterial sugar-based surfactants targeting lipid bilayers: mechanistic insights from molecular dynamics simulations

Sugar-based surfactants have been used in several applications due to their biocompatibility properties and low toxicity when compared to cationic detergents. These applications range from membrane protein crystallography to food industries, for example. Recently, a new family of alkyl deoxy glycosides with relevant antibacterial activities against Bacillus spp. and other pathogens was developed [1-3]. Experimental data shows that the deoxygenation of the sugar moiety leads to an increased surface activity of these molecules, which seems to modulate their antimicrobial properties. In this work, we used atomistic molecular dynamics simulations to characterize the micellization process of these glycosides in aqueous media and the adsorption of these micelles to a model phospholipid bilayer. We also simulated phospholipid/glycoside binary mixtures to analyze the effect of partitioning increased molar fractions of glycosides into the bilayer on its structural features. The results herein presented provide valuable information on the physical and biological properties of these molecules and may have implications on the design of new antibiotics with increased potency.

We thank QREN-COMPETE program for financing project FACIB (no. 21547) and Fundação para a Ciência e a Tecnologia for supporting strategic project Pest-OE/QUI/UI0612/2013 and PhD grant SFRH/BD/81017/2011. COST is acknowledged for funding through action CMST/COST-Action/CM1102.

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Harmonized tuning of nucleic acid and lectin binding properties with multivalent cyclodextrins for macrophage-selective gene delivery

Polycationic amphiphilic cyclodextrins (paCDs) have been shown to behave as efficient non-viral gene carriers paralleling the efficacy of commercial vectors towards a variety of cell lines. Their molecular framework and modular design allow the installation of saccharidic antennae to promote specific carbohydrate-protein interactions, thus potentially endowing them with selective targeting abilities. Yet, the presence of these additional functionalities onto the polycationic cluster may hamper paCD self-assembly and nucleic acid condensation. In this report we describe the influence of paCD mannosylation extent on paCD-pDNA nanocomplex stability as well as the consequences of varying glycotope density on mannose-specific lectin recognition and gene delivery capabilities. Herein we will present an exploration of the potential of this approach to simultaneously optimize both properties in order to modulate cell transfection selectivity [1].

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Lubricity of mucins as boosted by mucoadhesion

Mucins are a major macromolecular component of mucus gels that are known to protect underlying epithelial surfaces against pathogen and mechanical insult. Mucins and mucus gels are renowned for their unique lubricity, not only for biological tissues, but also for various engineering materials in aqueous environment. In this study, we present that complexation of mucins with synthetic polymers, in particular mucoadhesive polymers, can significantly improve the lubricating properties of mucins. For example, in acidic solution (pH 3.2) and low concentrations (0.1 mg/mL), the interaction of porcine gastric mucin (PGM) with chitosan led to a synergetic lubricating effect; while neither PGM nor chitosan showed any appreciable lubricity at PDMS-PDMS sliding contacts (coefficient of friction close to 1), the mixture of PGM-chitosan showed considerably improved lubricity and wear resistance of the adsorbed layers with the coefficient of friction as low as 0.011 at an optimum mixing ratio. Among many factors that are involved in this synergetic lubricity, mucoadhesive interaction of chitosan with PGM and acting as crosslinker within the adsorbed PGM layers appears to be most important, resulting in higher cohesion and lower interlayer chain interpenetration and bridging. Additionally, electrostatic attraction between polyanion (PGM) and polycation (chitosan), and consequently nullified overall charges may facilitate the adsorption onto nonpolar PDMS surface and further contributes to the enhanced lubricity. In this context, various polyamines have been employed to drive similar synergy at neural pH condition. Interestingly, among many polyamines tested, branched polyethyleneimine (PEI) was the only one that showed a clear improvement in lubricity, whereas all others, including linear PEI, poly(allylamine hydrochloride) (PAH) and poly(L-lysine) (PLL), have shown no or only minor effect. We propose that this is due to the different population of primary, secondary, and tertiary amines among the aforementioned polyamines, which play different roles in hydrogen bonding with PGM. In turn, this observation supports the claim that more than electrostatic attraction, mucoadhesion driven by hydrogen bonding plays the most dominant role in the interaction between PGM and chitosan.

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Chemical tools to study carbohydrate-DNA minor groove interactions

The understanding of structural details involved in molecular recognition processes has vital importance to influence and modulate biological events. In this context, carbohydrate recognition is nowadays a key research area, due to its implication in multiple occurrences with biomedical relevance. It's well known that hydrogen bonds and CH-π interactions are main driving forces of carbohydrate recognition by lectins. In contrast, the binding process and recognition of DNA minor groove by carbohydrates is not known. The ability of carbohydrates to form hydrogen bonds could be considered when interacting with the base pair donor and acceptor centres and the phosphate backbone. Moreover, one way to increase the affinity and directionality of these forces could be the use of hydrogen bonding cooperativity. Based on this, the aim of our work is to develop new chemical tools that help to understand the process of DNA recognition by carbohydrates at molecular level and also the influence of hydrogen bond cooperativity in that interaction. The goal is to design a vector capable of carrying different carbohydrates to the DNA minor groove, study their interactions and finally quantify the hydrogen bond cooperativity in the recognition process. Our group has experience in using oligoamide type vectors. Those compounds were very useful and gave us much information about that interaction process. However, it was not possible to quantify interaction and hydrogen bond cooperativity. So, in order to reach this purpose, we have design a new vector based on the well-known Hoechst 33258, with some modifications made by Nielsen and Jacobsen. Therefore, the structure of our ligands is an amino aryl bis-benzimidazole with a carbohydrate linked by an amide bond. The different carbohydrates we are going to study are beta anomers of mannose and glucose of both series D and L. Thanks to this design, we can create derivatives with a cooperative hydrogen bonding network (mannose derivatives) or without it (glucose derivatives) and compare their binding properties with different DNA sequences. Here, we present the synthesis and preliminary interaction studies of beta-D-mannose Hoechst derivative. We have developed a linear microwave assisted synthesis to achieve an efficient route. Thanks to that, we were able to obtain the desired compound only in the beta form. Initial studies of their interaction with fish sperm DNA using different biophysical techniques like NMR, circular dichroism and UV-VIS spectroscopy will be shown.

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Sugars Shapes & Peptide Folds: Synthetic Sugar Mimetics that Modulate Protein Function

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 using these to understand 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.

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Synthesis of trimeric coiled coils presenting lactose as glycoclusters

Multivalent carbohydrates continue to be of interest to researchers as they can bind to lectins with higher potency and selectivity than monovalent carbohydrates. They can have potential applications as modulators of biological functions. For example, they have potential as inhibitors of glycan crosslinking lattices at cell surfaces, the latter which can lead to stronger and more prolonged cell signalling. This presentation deals with the design and synthesis of trimeric coiled coil scaffolds for the multivalent display of lactose residues, which have potential as glycocluster ligands for galectins and plant lectins. Monomeric glycopeptides have been synthesised and these undergo self-assembly into trimeric structures within aqueous conditions. Analytical ultracentrifugation and circular dichrosim spectroscopy techniques have been used to support the trimerisation of these glycopeptides and assembly to give the new glycoclusters.

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Multivalent glycocyclopeptides: synthesis and applications

Synthetic glycoclusters and glycodendrimers have stimulated increasing interests over the past decade. Among the large variety of multivalent scaffolds reported so far, our group is focusing on cyclopeptide-based glycoconjugates for diverse biological applications. In this context, well-defined structures with various composition, size and sugar density were prepared in a controlled manner using chemoselective procedures (i.e. oxime ligation, Huisgen 1,3-dipolar cycloaddition, thiol-ene). Here we present the synthesis of several compounds and their biological properties.

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Fluorescent Multivalent Glycan Probes for Glycobiology Research

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Glycopeptidenanofibers for chondrogenic differentiation

Glycosaminoglycans (GAGs) are a group of extracellular matrix (ECM) polysaccharides which are unbranched and are involved in numerous biological activities. They are important as molecular co-receptors in cell–cell interactions via their ability to interact with ECM proteins and peptide growth factors. GAGs have vital roles in the binding and activation of growth factors in cell signal transduction required for biological development such as cell adhesion, migration, growth and differentiation. Here, we have inspired from GAGs to induce chondrogenic differentiation of cells as preliminary steps of articular cartilage tissue regeneration studies. Articular cartilage covers the bony surface of joints. Its function is to provide a low friction surface enabling the joint to withstand weight bearing through the range of motion needed to perform daily activities as well as athletic endeavors. Articular cartilage enables the knee to tolerate shear forces and absorb shock and loads up to 20 times the body's weight. Therefore, articular cartilage defects impact daily activities of people negatively. However, cartilage tissue has low regeneration capacity. Thus, chondrogenic differentiation is of interest to researchers from different areas. Our motivation is to create cartilage mimicking ECM by using glyco-conjugated peptide nanostructures in order to induce differentiation of cells into cartilage cells, and to obtain a biocompatible material that can be used for regeneration of articular cartilage defects. In this study, amphiphilic glycopeptides were succesfully synthesized and characterized. Morphological and chemical analysis of the peptide networks were carried out. Preliminary cell culture experiments revealed that cartilage ECM mimetic glycopeptide nanonetworks trigger better and faster chondrogenic differentiation compared to positive control (Hyalgan®/peptide nanonetwork) and negative controls (TCP and nonbioactive PA) even in the absence of chondrogenic medium.

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Multivalent lectins and cell surfaces: labeling and dynamics

A large number of pathogenic microorganisms display receptors for specific recognition and adhesion to the glycoconjugates present on human tissues. In addition to membrane-bound adhesins, soluble lectins are involved in infections caused by the bacteria Pseudomonas aeruginosa and Burkholderia cepacia and by the fungus Aspergillus fumigatus that are responsible for hospital-acquired diseases. Accumulated knowledge about the structures of the lectins and the interactions with host glycoconjugates has lead to the design of powerful glyco-derived inhibitors that can serve as antimicrobial therapeutic agents, as a complement to or an alternative to antibiotic therapy. Design of glycosylated chips, liposomes, fullerenes and other nanoglycoparticles have provided information on multivalent interaction between receptors and cell surfaces. This also results in development of nanomaterials that can be used in diagnostic applications. Furthermore, the multivalency of lectin is proposed to play a role in their strong avidity for glycosylated cell surfaces and also in their ability to affect membrane dynamics by clustering glycosphingolipids. Bacterial lectins are able to bind to glycoconjugates on human tissues and are therefore thought to be involved in the first step of infection. The role of lectins in membrane invagination indicates that they could also play a role in internalization of intracellular pathogens.