American Chemical Society
Division of Carbohydrate Chemistry

Newsletter

Fall 2009

2008–2009 Division Officers

Past Chairman
Dr. Gillian Eggleston
Research Chemist/Lead Scientist
SRRC-USDA-ARS
1100 Robert E. Lee Blvd.
New Orleans, LA 70124, USA
Phone: 504-286-4446
Fax: 504-286-4367
Email: gillian@srrc.ars.usda.gov

Treasurer
Professor Zbigniew J. Witczak
Department of Pharmaceutical Sciences
Nesbitt School of Pharmacy
Wilkes University
84 W. South Street
Wilkes-Barre, PA 18766, USA
Phone: 570-408-4276
Fax: 570-408-7828
Email: witczak@wilkes.edu

Chairman
Dr. Muthiah Manoharan
VP Drug Discovery
Alnylam Pharmaceuticals
300 Third Street
Cambridge MA 02142, USA
Phone: 617-551-8319
Fax: 617-551-8301
Email: mmanoharan@alnylam.com

Secretary/Newsletter Editor
Professor Todd L Lowary
Department of Chemistry
E2-52A Gunning-Lemieux Chemistry Centre
The University of Alberta
Edmonton, AB, T6G 2G2, Canada
Phone: 780-492-1861
Fax: 780-492-7705
Email: tlowary@ualberta.ca

Chairman Elect
Professor Dev P. Arya
461 Hunter
Department of Chemistry
Clemson University
Clemson, SC 29634, USA
Phone: 864-656-1106
Fax: 864-656-6613
Email: dparya@clemson.edu

Website Maintenance
Professor Xi Chen
Department of Chemistry
University of California Davis
One Shields Avenue, CA 95616
Phone: 530-754-6037
Fax: 530-752-8995
E-mail: chen@chem.ucdavis.edu

Program Chair
Professor Todd L Lowary
Department of Chemistry
E2-52A Gunning-Lemieux Chemistry Centre
The University of Alberta
Edmonton, AB, T6G 2G2, Canada
Phone: 780-492-1861
Fax: 780-492-7705
Email: tlowary@ualberta.ca

Councilor
Professor Derek Horton
Department of Chemistry
American University
4400 Massachusetts Ave., NW
Washington, DC 20016, USA
Phone: 202-885-1767
Fax: 202-885-1752
Email: carbchm@american.edu

2008–2009 Division Officers

Councilor
Dr. John R. Vercellotti
V-Labs, Inc.
423 N. Theard St.
Covington, LA 70433, USA
Phone: 985-893-0533
Fax: 985-893-0517
Email: v-labs@v-labs.com

Member-at-Large
Professor Alexei V. Demchenko
Department of Chemistry and Biochemistry
University of Missouri - St. Louis
434 Benton Hall (MC27)
One University Boulevard
St. Louis, MO 63121, USA
Phone: 314-516-7995
Fax: 314-516-5342
Email: demchenkoa@umsl.edu

Alternate Councilor
Professor Anthony S. Serianni
Department of Chemistry and Biochemistry
University of Notre Dame
Notre Dame, IN 46556-5670
Phone: 219-631-7807
Fax: 219-631-6924
Email: serianni.1@nd.edu

Member-at-Large
Professor Peter H. Seeberger
Laboratory for Organic Chemistry
ETH Zürich, HCI F315
Wolfgang-Pauli-Str. 10,
8093 Zürich, Switzerland
Phone: 41-1-633-2103
Fax: 41-1-633-1235
Email: seeberger@org.chem.ethz.ch

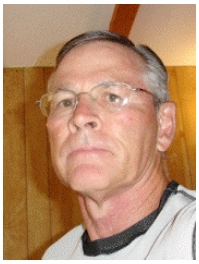
Alternate Councilor
Professor Walter Szarek
Department of Chemistry
Queen's University
Kingston, ON K7L 3N6, Canada
Phone: 613-533-2643
Fax: 613-533-6532
Email: szarekw@chem.queensu.ca

Member-at-Large
Dr. Arland T Hotchkiss
Plant Physiologist/Lead Scientist
USDA-ARS, ERRC
600 E. Mermaid Lane
Wyndmoor, PA 19038, USA
Phone: 215-233-6448
Fax: 215-233-6406
Email: arland.hotchkiss@ars.usda.gov

Member-at-Large
Dr. Douglas M. Van Thorre
President/CTO
Biorefining, Inc.
4979 Olson Memorial Highway
Golden Valley, MN 55422, USA
Phone: 763-746-0206
Fax: 763-746-0201
Email: dvthorre@biorefining.com

Wolfrom/Isbell/New Investigator Awards Committee
Professor Zbigniew J. Witczak
Department of Pharmaceutical Sciences
Nesbitt School of Pharmacy
Wilkes University
84 W. South Street
Wilkes-Barre, PA 18766, USA
Phone: 570-408-4276
Fax 570-408-7828
Email: witczak@wilkes.edu

2008–2009 Division Officers



Wolfrom/Isbell/New Investigator Awards Committee
Dr. Phillip Dan Cook
Carlsbad Pharmaceuticals, Inc.
1447 Summit Ave
Cardiff-by-the-Sea, CA 92007
Phone: 760-586-5009
Email: pdancook@hotmail.com

Wolfrom/Isbell/New Investigator Awards Committee
Professor Hans Vliegenthart
Bijvoet Center
Division Bioorganic Chemistry
Utrecht University, Padualaan 8,
NL 3584 CH Utrecht
Phone: 31-30-253-2168
Fax: 31-30-254-0980
Email: j.f.g.vliegenthart@chem.uu.nl

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New Membership Application

I wish to enroll as a member of the ACS Division of Carbohydrate Chemistry.
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$12.50 per year thereafter; $7.00 for students.

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Todd L. Lowary
Department of Chemistry
E2-52A Gunning-Lemieux Chemistry Centre
The University of Alberta
Edmonton, AB, T6G 2G2, Canada
Phone: 780-492-1861
Fax: 780-492-7705
Email: tlowary@ualberta.ca

Wolfrom/Isbell/New Investigator Award Dinner

Please join us for the Wolfrom/Isbell/New Investigator Award Dinner, which will be held Monday, August 16, 2009 from 6:00–10:00 PM at the The University Club of Washington, DC, 1135 Sixteenth Street, N. W. Washington, D.C. 20036. Tickets are $50 and can be purchased online when registering or from Todd Lowary at the meeting. The dinner will honor this year's winners of these awards: Waldemar Priebe (Wolfrom Award), George O'Doherty (Isbell Award) and Xuefei Huang (New Investigator Award).

Future Newsletters

The Carbohydrate Division Newsletter is published twice a year, just before the two annual National ACS meetings. If you have items for inclusion in future newsletters, please send this information to: Todd L. Lowary, Department of Chemistry, E2-52A Gunning-Lemieux Chemistry Centre, The University of Alberta, Edmonton, AB, T6G 2G2, Canada, Phone: 780-492-1861, Fax: 780-492-7705, Email: tlowary@ualberta.ca.

Future Divisional Symposia

If you have ideas for future Carbohydrate Division symposia, these can be directed to Todd L. Lowary, Department of Chemistry, E2-52A Gunning-Lemieux Chemistry Centre, The University of Alberta, Edmonton, AB, T6G 2G2, Canada, Phone: 780-492-1861, Fax: 780-492-7705, Email: tlowary@ualberta.ca.

Solicitation of Nominations for Division Awards

The Division is soliciting nominations for the 2009 Melville L. Wolfrom Award, Horace S. Isbell Award and New Investigator Award, which will be awarded at the Fall 2009 meeting in Washington DC.

- *The Melville L. Wolfrom Award* acknowledges outstanding service to the Division and to the field of carbohydrate chemistry.
- *The Horace S. Isbell Award* acknowledges excellence in and promise of continued quality of contribution to research in carbohydrate chemistry. The winner must be under the age of 41 at the time of the award.
- *The New Investigator Award* acknowledges and encourages outstanding contributions to research in carbohydrate chemistry by scientists in their first independent faculty position.

Visit membership.acs.org/C/CARB/awards.html for nomination forms.

NOTE: NOMINATION DEADLINE IS SEPTEMBER 15, 2009

Upcoming National ACS Meeting

239th National Meeting

March 21–25, 2010, San Francisco, CA

Scheduled Carbohydrate Division Symposia Include:

Sustainability of the Sugar and Sugar-Ethanol Industries

Young Investigators in Glycoscience

General Papers: Glycobiology

General Papers: Polysaccharides

General Papers: Synthetic Chemistry

Posters

The deadline for Carbohydrate Division abstracts is October 19, 2009

Other Upcoming Meetings

XXV International Carbohydrate Symposium

August 1–August 6, 2010 – Tokyo, Japan

Visit http://www.bilingualgroup.co.jp/ics2010 for more information.

Program Sponsors

A big "Thank You" to the sponsors of our program.

The following companies and organizations have provided financial support for our program

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238th American Chemical Society Meeting

Washington, DC
August 16–20, 2009

Division of Carbohydrate Chemistry

Technical Program

238th ACS Meeting Carbohydrate Division Program

SUNDAY MORNING

Section A

Walter E. Washington Convention Center 101

Wolfrom, Isbell, New Investigator Awards Symposium

M. Manoharan, *Presiding*

G. Eggleston, *Organizer, Presiding*

8:00 Introductory Remarks.

8:05 1. 1,3,2-oxathiaphospholane ring opening approach to the synthesis of analogs of nucleoside 5'-*O*-polyphosphates. D. Blaziak, P. Guga, A. Jagiello, A. Nowicka, A. Pietkiewicz, **W. J. Stec**

8:40 2. Anomeric hydroperoxides: Synthesis, enantioselective epoxidation. **M. C. Chmielewski**

9:15 3. Natural thio-sugars and their bioisostere functionalizations. **Z. J. Witczak**

9:50 Intermission.

10:05 4. Glycals: Conformational models and versatile synthons for anthracycline glycosides**. D. Horton**

10:40 5. Galectins and their role in high-grade glioma tumor progression. **C. Conrad**, T. Madden, X. Sheng, W. Priebe

11:15 6. Drug discovery in academia: A chemist in the biologist's cookie jar. **W. Priebe**

Section B

Walter E. Washington Convention Center 103B

General Papers: Polysaccharides

T. L. Lowary, *Organizer, Presiding*

9:00 7. *Caulobacter crescentus* growth in xylan and cellobiose: Effect on microbial plant polysaccharide metabolism. **G. R. Periyannan**, B. Riegel, D. Gamage

9:20 8. Simulation of force spectroscopy for polysaccharides with a replica-exchange method enhanced umbrella sampling approach. **X. Zeng**, H. Hu, H.-X. Zhou, P. Marszalek, W. Yang

9:40 9. Understanding the polysaccharide chain in ionic liquid: A molecular dynamics study. **H. Liu**, S. Singh, B. Holmes, B. A. Simmons

10:00 10. Gum arabic-chitosan composite biopolymer scaffolds for bone tissue engineering. **R. A. Silva**

10:20 Intermission.

10:40 11. Preparation and characterization of poly(lactic acid)/chitosan copolymers. **A. C. Fonseca**, P. N. Simões, M. H. Gil

11:00 12. Controlled grafting modification of chitosan via living radical polymerization. **J. F. J. Coelho**, M. Gil

11:20 13. Influence of steaming time on steam explosion pretreatment of Lespedeza stalks (*Lespedeza crytobotrya*): Characteristics of degraded cellulose. K. Wang, J. Jiang, **F. Xu**, **R. Sun**

11:40 14. Preparation and properties of sodium carboxymethyl cellulose-hyaluronic acid-carboxymethyl chitosan blend films. **X. Zhao**, X. He, L. Yang

SUNDAY AFTERNOON

Section A

Walter E. Washington Convention Center 101

Wolfrom, Isbell, New Investigator Awards Symposium

T. L. Lowary, Presiding

G. Eggleston, Organizer, Presiding

1:15 15. Endoglycosidase-catalyzed transglycosylation: Mechanistic studies and synthetic applications. **L.-X. Wang**

1:50 16. Carbohydrate-based drug discovery. **C.-H. Wong**

2:25 17. Magnetic glyco-nanoparticles, a useful tool for detection and differentiation of bacteria and cancer cells. **X. Huang**, K. El-boubbou, M. N. Kamat

3:00 Intermission.

3:15 18. Mechanistic studies of C-4 deoxygenation in the biosynthesis of desosamine. **H.-W. Liu**

3:50 19. Formation of C–C bonds via catalytic hydrogenation: Construction of carbohydrates and polyketides. **M. J. Krische**

4:25 20. De novo synthesis in carbohydrate chemistry. **G. A. O'Doherty**

MONDAY MORNING

Section A

Walter E. Washington Convention Center 101

Synthetic Carbohydrate Chemistry: A Symposium in Memory of Nikolay Kochetkov and Per Garegg

T. L. Lowary, Organizer

A. V. Demchenko, Organizer, Presiding

8:00 Introductory Remarks.

8:05 21. Conjugate vaccines from synthetic carbohydrate antigens. **P. Pavol Kováč**

8:40 22. GPI anchors: WHY and HOW the complex molecules are being synthesized. **A. V. Nikolaev**

9:15 23 Synthesis of anthrax dissacharides: Application toward an anthrax detection system. **H. Y. Wang**, H. Guo, G. A. O'Doherty

9:35 24. Half of sugar chemistry resides at the anomeric carbon. **S. Hanessian**

10:10 Intermission.

10:30 25. Development of novel one-pot carbohydrate synthesis methodologies. **X. Huang**

11:05 26. Novel sugar-based heterocycles via the addition of aromatic imines to glycals. **C. H. Marzabadi**, P. Dobbelaar, K. Konchalski, K. N. Brogden

11:25 27. New schemes in oligosaccharide synthesis. **N. N. Nifantiev**, N. E. Ustyuzhanina, Y. E. Tsvetkov, B. S. Komarova, V. B. Krylov, Y. V. Mironov, A. G. Gerbst

238th ACS Meeting Carbohydrate Division Program

MONDAY AFTERNOON

Section A

Walter E. Washington Convention Center 101

Synthetic Carbohydrate Chemistry: A Symposium in Memory of Nikolay Kochetkov and Per Garegg

A. V. Demchenko, Organizer

T. L. Lowary, Organizer, Presiding

1:45 28. Chemoenzymatic synthesis of heparin and heparin oligosaccharides. **R. J. Linhardt**, J. Liu, J. S. Dordick, S. Mousa

2:20 29. Oligosaccharide synthesis for glycobiology. **Y. Ito**

2:55 30. Synthesis of carbohydrates linked to heterocyclic compounds. **E. S. H. El Ashry**

3:15 31. Synthesis of oligosialic acids. **T. Takahashi**

3:50 Intermission.

4:10 32. Thioglycosides as glycosyl donors: Synthesis of complex microbial carbohydrate structures. **S. Oscarson**

4:45 33. Synthetic oligosaccharides as vaccine candidates for microbes classified as bioterrorism agents. **G.-J. Boons**

MONDAY EVENING

Section A

Walter E. Washington Convention Center Hall D

Sci-Mix

T. L. Lowary, Organizer

8:00–10:00

Posters **48**, **50**, **54**, **58–59**, **62–64**, **66–69**, **73–77**, **79–84**, **86–91**, **93–97**, **99**, **100**, **102**, **104**, **105**. See subsequent listings.

238th ACS Meeting Carbohydrate Division Program

TUESDAY MORNING

Section A

Walter E. Washington Convention Center 101

RNA Targeting - Nucleic Acids and Analogs

Cosponsored by BIOL, MEDI, and ORGN

M. Manoharan and D. H. Appella, Organizers

8:30 Introductory Remarks.

8:35 34 RNA targeting by siRNAs for therapeutics. **M. Manoharan**

9:05 35. Crystallographic analyses and structure/activity correlations of siRNA modifications. **M. Egli**

9:35 36. Novel and structurally biased backbone modifications of nucleic acids. **V. A. Kumar**

10:05 Intermission.

10:15 37. PNA analogs with potential for selective RNA targeting. **K. N. Ganesh**

10:45 38. Multivalent binding oligomers to target TAR. **D. H. Appella**

11:15 39. Synthesis and characterization of new siRNA prodrugs. **R. Johnsson**, J. G. Lackey, M. J. Damha

11:35 40. Efficient GeRP-mediated oral delivery of siRNA to macrophages modulates inflammation in mice. M. Aouadi, G. J. Tesz, S. M. Nicoloro, M. Chouinard, M. Wang, E. Soto, M. P. Czech, **G. Ostroff**

TUESDAY AFTERNOON

Section A

Walter E. Washington Convention Center 101

RNA Targeting - Novel Ligands

Cosponsored by BIOL, MEDI, and ORGN

M. Manoharan and D. H. Appella, Organizers

1:30 Introductory Remarks.

1:35 41. Modified regions of bacterial ribosomes as target sites for new ligands. **C. S. Chow**

2:05 42. Helix-threading ligands for targeting RNA. **P. A. Beal**

2:35 43. Exploring RNA recognition processes using fluorescent nucleosides. **Y. Tor**

3:05 44. Targeting the hepatitis C virus internal ribosome entry site RNA. **T. Hermann**

3:35 Intermission.

3:45 45. Targeting RNA with aminosugars. **D. P. Arya**, N. Ranjan

4:15 46. A dynamic combinatorial approach to the challenge of sequence-selective RNA recognition. **B. L. Miller**

4:45 47. Using an RNA motif-ligand database to help rationally target RNA with small molecules. **M. D. Disney**

5:15 Concluding Remarks.

Section B

Walter E. Washington Convention Center Hall D

General Posters

T. L. Lowary, Organizer

12:00–2:00

48. Biophysical characterization and conformational analysis of antiproliferative factor (APF): A novel anticancer lead compound. **K. M. Adams**, P. Kaczmarek, Y.-C. Lee, S. K. Keay, J. J. Barchi Jr.

49. Biosynthetic production of N-linked glycans coupled with in vitro enzymatic processing to produce homogenous high mannose, hybrid, and complex type oligosaccharides. **B. S. Hamilton**, R. Chen, M. Pawlicki, T. J. Tolbert

50. Carbohydrate separation through boron affinity saccharide electrophoresis. **J. S. Fossey**, T. D. James, J. M. van den Elsen, M. P. Pereira Morais

51. Interactions between transition metal particles and biopolymer chains modify the helical structure of amylose. **P. Bernazzani**, B. A. McKinley

52. Glucosylation of raffinose via glucansucrase acceptor reactions. **G. L. Cote**, C. A. Dunlap, K. E. Vermillion

53. **WITHDRAWN**

54. Structural and biochemical characterization of the fungal GPI transamidase. **Y. Varma**, M. Ehrenwerth, J. Klebba

55. Studies of heparin-protein interaction using click chemistry. **S. Bera**

56. ZnSe nanoparticles insertion modify the physical properties of starch-polyethylene blends. **P. Bernazzani**, D. P. Obulasetty

57. Clearing a path for nerve growth by the immobilized chondroitinase. **Z. Xiao Jr.**, R. J. Linhardt

58. Synthesis of ^{13}C labeled UDP-nucleotides for the enzymatic preparation of ^{13}C labeled oligosaccharides. **S. Masuko**, M. Weiwer, J. H. Kim, R. J. Linhardt

59. Activity study on several mutants heparin lyase II. **W. Zhao**, Z. Zhang, Z. Xiao, M. Cygler, R. J. Linhardt

60. Studying galactosyltransferases that are important for the viability of *Mycobacterium tuberculosis*. **V. R. Annamalai**, J. F. May, R. Splain, C. Brotschi, L. L. Kiessling

61. Analysis of isolated and purified *Staphylococcus aureus* capsular polysaccharide via monoclonal antibodies, mass spectrometry, and nuclear magnetic resonance spectroscopy. R. Maxon, **J. M. Wells**, A. D. Hunter, M. Zeller, D. D. Fagan

62. Application of crosslinked rice starches as drug delivery matrices in monolithic tablets. C. Peluso, **F. O. Onofre**, G. Mendez-Montealvo, Y.-J. Wang

63. Disaccharide composition analysis of glycosaminoglycans from 4 human embryonic stem cells. **B. Li**, Z. Zhang, A. V. Nairn, K. W. Moremen, S. Dalton, R. J. Linhardt

64. Expression and characterization of enzymes for bioenzymatic sythesis of heparin. **P. A. Paul**, J. S. Dordick, R. J. Linhardt, J. Liu, W. Zhao

65. **WITHDRAWN**

66. Hydroxypropylated starches of varying amylose contents as sustained release matrices in monolithic tablets. **F. O. Onofre**, Y.-J. Wang

67. Intramolecular glucosamine α-glycosylation: Mycothiol. **K. Ajayi**, V. Thakur, R. C. Lapo, S. Knapp

68. Labeling of lipoglycans with quantum dots. **M. Gonzalez-Moa**, C. Morales , S. A. Svarovsky

69. Multivalent presentation of tumor-associated carbohydrate antigen using gold nanoparticles as scaffold for immunotherapeutic applications. **R. P. Briñas**, A. Sundgren, M. Maetani, K. Rittenhouse-Olson, P. Sahoo, S. Morey, A. Houghton, J. J. Barchi Jr.

70. Nonhydrolyzable, lipid-linked inositol glycan with potential anticancer activity. **M. Goel**, M. d'Alarcao

71. Optimization of GeRP-mediated siRNA transfection. **S. Kahlon**, E. Soto, G. Ostroff

72. Probing the origin of diastereoface selectivity in a SmI_2-mediated pinacol cyclization. **K. Ding**, A. Kornienko, D. I. Turner, M. d'Alarcao

73. Solution structure of a central fragment of the tumor antigen Le^aLe^x. **M. Svensson**, T. A. Jackson, A. Wang, G. Widmalm, F.-I. Auzanneau

74. The stereoselective synthesis of C-linked neuraminic acid oligosaccharides. **J.-H. Kim**, S. Masuko, T. Poore, S. Bera, R. J. Linhardt

75. Synthesis of three-component cancer vaccines and immunotherapy studies in MUC1.tg mice. **P. S. Thompson**, V. Lakshminarayanan, T. Buskas, S. J. Gendler, G. J. Boons

76. Synthesis of glycosidase-inhibiting bicyclic iminosugars. **A. S. McComb**, D. R. Adams, R. H. Wightman

77. Antioxidant activities of two fractions of water-soluble polysaccharide from mung bean (Vigna Radiata L.) hull by ultrasonic assisted extraction. F.-R. Lai, H. Wu, X.-F. Li, Q.-B. Wen, **H.-N. Xiao**

78. Carbohydrate uptake and utilization of *Clostridium tyrobutyricum* ZJU 8235. L. Jiang, **J. Wang**, S. Liang, P. Cen, Z. N. Xu

79. Synthesis and biological evaluation of glycoporphyrins. **J. P. C. Tome**, L. M. O. Lourenço, M. G. P. M. S. Neves, J. A. S. Cavaleiro

80. Analysis of heparin microarrays using MALDI-TOF-TOF allows for high-throughput analysis of heparin degradation. **H. E. Stansfield**, T. N. Laremore, W. Zhao, J. S. Dordick, R. J. Linhardt

81. Biochemically engineered heparin. **Z. Wang**, Z. Zhang, W. Zhao, F. Zhang, R. J. Linhardt

82. Chemoenzymatic synthesis of a new class of macrocyclic oligosaccharides. **S. Muthana**, X. Chen

83. Conformational studies of lacto-N-fucopentaose 2 using NMR spectroscopy and molecular simulations. **E. Säwén**, F. Hinterholzinger, C. Landersjö, G. Widmalm

84. Elucidating the role of a hydrogen bond donor at the 2'-position of the 3'-linked departing nucleoside in transesterification by large ribozymes: Hydrolytic reactions of 2',3'-*O*-methyleneadenosin-5'-yl 5'-*O*-methyluridin-3'-yl 5'-*O*-methyl-2'-trifluoroacetamido-2'-deoxyuridin-3'-yl phosphate. **T. A. Lönnberg**, M. Laine

85. Solution structures of chemoenzymatically synthesized heparin and its precursors. **Z. Zhang**, S. A. McCallum, J. Xie, L. Nieto, F. Corzana, J. Jime´nez-Barbero, J. Liu, R. J. Linhardt

86. Analysis of pharmaceutical heparins and potential contaminants using ^{1}H-NMR and PAGE. **Z. Zhang**, B. Li, J. Suwan, F. Zhang, Z. Wang, H. Liu, B. Mulloy, R. J. Linhardt

87. Chondroitin lyase action pattern study using LC-MS. **Z. Zhang**, Y. Park, M. Kemp, W. Zhao, M. Cygler, Y. S. Kim, R. J. Linhardt

88. Distribution of lignin and cellulose in cell walls of *Cornus alba*. **F. Xu**, J. Mao, X. Zhong, H. Zhao

89. Lessons learned from the contamination of heparin. H. Liu, **Z. Zhang**, R. J. Linhardt

90. Regioselective glycosylation of mannose diols: Studies toward a more efficient synthesis of high mannose type oligosaccharides. **J. M. Kalikanda**, Z. Li

91. Computational analysis of carbohydrates processing for *Enterococcus faecalis* and Escherichia coli. **J. Shelton**, B. L. Bailey, K. Watkins, C. Saito, J. Lack, E. Love, T. James, E. Benjamin III, E. Benjamin

92. Structural specificity of gp120 carbohydrates for binding to HIV-fusion blocking cyanobacterial proteins determined by NMR and other biophysical techniques. **S. S. U. Hussan**, A. B. Shah, C. A. Bewley

93. Synthesis and properties of amide modified RNA analogs. **P. Tanui**, C. Selvam, S. Thomas, J. Abbott, M. Kullberg, E. Rozners

94. Glycosylation characterization of recombinant intrinsic factor. **L. Chi**, C. S. Ramsay, J. R. Fishpaugh, Y. Pan, G. J. Davis

95. Purification of carbohydrates by medium pressure liquid chromatography. **J. E. Silver**, E. Bilger, T. R. Crea, R. Pipes

96. Boronic acid-modified TTP analogs for the selection of DNA-based aptamers for glycoproteins. **Y. Cheng**, S. Jin, S. Zheng, C. Dai, M. Li, B. Wang

97. Peptide nucleic acid analogs for sequence selective RNA recognition. **O. Muse**, M. Li, E. Rozners

98. Carbohydrate coating of carbon nanotubes for detection of cell secretion. **J. Ma**, S. Ng, H. G. Sudibya, P. Chen, X.-W. Liu

99. Development of an indium-mediated tandem carbon-carbon bond forming reaction: Application to the synthesis of C-aryl glycosides. **T. G. Minehan**, J. A. Moral, S.-J. Moon, S. Rodriguez-Torres

100. One-pot rhodium-catalyzed aziridination and ring-opening of glycal: A direct access to 2-amino sugars and its application to synthesis of sialic acids. X. Liu, **R. Lorpitthaya**

101. Computationally and experimentally derived general rules for fragmentation of various glycosyl bonds in sodium adduct oligosaccharides. H. Suzuki, **K. Fukui**

102. Synthesis of novel photoreactive PFPA-carbohydrates for study of carbohydrate-protein interactions. **L. Deng**, O. Norberg, S. Uppalapati, M. Yan, O. Ramstrom

103. The synthesis of macrocyclic compounds based on glucuronic acid as putative tumor cell migration inhibitors. **D. Yan**

104. Facile synthesis and antitumor cell activity of Se-containing nucleosides. **L. Lin**, J. Sheng, R. K. Momin, Q. Du, Z. Huang

105. Selenium derivatization of human telomeric DNA for structure and function study. **T. Tian**, J. Sheng, X. Zhou, S. Wang, Z. Huang

WEDNESDAY MORNING

Section A

Walter E. Washington Convention Center 101

Glycotherapeutics: Synthesis and Biology

D. I. Freedberg, Organizer

J. J. Barchi Jr., Organizer, Presiding

8:10 106. Biosynthesis of O-glycans and cost effective strategies for the synthesis of mucin O-glycans. **K. L. Matta**, V. Kumar, S. K. Khaja, J. Xue

8:45 107. Developments in the total synthesis of M. tuberculosis LAM prototype. **B. Fraser-Reid**, R. V. Changalvala, S. Ray Chaudhuri

9:20 108. Application of surface plasmon resonance (SPR) in glycobiology: Characterization of molecular interactions between GAGs and proteins. **F. Zhang**, R. J. Linhardt

9:40 109. *Caenorhabditis elegans* bus-2 mutant reveals a new class of O-glycans involved in bacterial resistance. E. Palaima, C. E. Costello, J. Hodgkin, M. Gravato-Nobre, N. Leymarie, **J. Cipollo**

10:15 Intermission.

10:30 110. Dissecting the glycobiologic regulators of prostate tumor metastasis. **C. J. Dimitroff**

11:05 111. Design, synthesis, and screening of a library of peptidyl-oligo(boroxole) receptors for complex oligosaccharides in physiological conditions. **A. Pal**, M. Bérubé, D. G. Hall

11:25 112. Glycosignature analysis of complex carbohydrates. **S. A. Svarovsky**

Section B

Walter E. Washington Convention Center 143A

General Papers: Synthetic Chemistry

T. L. Lowary, Organizer, Presiding

8:30 113. Click assisted synthesis of glycosulfopeptide mimetics of P-selectin glycoprotein ligand-1. **Y. Vohra**, F. L. van Delft, G. J. Boons

8:50 114. Solid-phase N-linked glycopeptide and glycoconjugate synthesis. R. Chen, B. S. Hamilton, J. Xiao, M. Pawlicki, **T. J. Tolbert**

9:10 115. Imidazolium cation supported solution-phase synthesis of carbohydrates. **A. K. Pathak**

9:30 116. Kinetic and thermodynamic characterization of an enzyme that modifies the 2-deoxystreptamine ring common to all aminoglycoside antibiotics. **A. L. Norris**, E. H. Serpersu

9:50 117. Modular synthesis of heparan sulfate fragments using orthogonally protected disaccharide building blocks. **S. Arungundram**, K. Al-Mafraji, J. Asong, A. Venot, G.-J. Boons

10:10 Intermission.

10:30 118. Conformational analysis of nucleosides and nucleotides: An update of the PSEUROT program. **S. M. Graham**

10:50 119. **WITHDRAWN**

11:10 120. Step economy process for the efficient and stereocontrolled construction of biotinylated chondroitin sulfate oligosaccharides. **A. Vibert**, C. Lopin-Bon, J.-C. Jacquinet

11:30 121. Studies of the racemization of Tn-antigen containing glycopeptides via solid-phase peptide synthesis. **Y. Zhang**

WEDNESDAY AFTERNOON

Section A

Walter E. Washington Convention Center 101

Glycotherapeutics: Synthesis and Biology

J. J. Barchi Jr., Organizer

D. I. Freedberg, Organizer, Presiding

1:45 122. Immunological responses from an entirely carbohydrate antigen: Design of synthetic vaccines based on Tn-PS A1 conjugates. **P. R. Andreana**

2:20 123. Functional glyco-capturing macroligand for glyco-proteomics and glycomics. **X.-L. Sun**, S. Chalagalla, S. Narla

2:40 124 Novel glycan clusters as epitope mimics of the HIV-neutralizing antibody 2G12. **L.-X. Wang**

3:15 125. Potent antiviral activity of the lectin griffithsin. **B. O'Keefe**, B. Giomarelli, C. Saucedo, P. McCray, C. Lear, E. Olinger, K. E. Palmer, R. Shattock, J. B. McMahon

3:50 Intermission.

4:00 126. Targeted antigen delivery using β-(1→3)-glucan particles. **S. Nagarajan**, H. Huang, E. Soto, S. Levitz, G. Ostroff

4:20 127. Recent developments in pentenyl based glycosylations: Applications to biologically relevant oligosaccharides. **J. C. Lopez**, A. M. Gomez, C. Uriel, J. A. Ventura, B. Fraser-Reid

4:55 128. 1,5-C-Thio-sugars as selective inhibitors of thioredoxins. **Z. J. Witczak**

THURSDAY MORNING

Section A

Walter E. Washington Convention Center 101

General Papers - Glycobiology and Computation

T. L. Lowary, Organizer

M. M. Kuttel, Presiding

9:00 129. Mechanism of cellulose hydrolysis by inverting GH8 endoglucanases: A QM/MM metadynamics study. **L. Petersen**, A. Ardèvol, C. Rovira, P. J. Reilly

9:20 130. Molecular modeling of bacterial exopolysaccharides. **M. M. Kuttel**, R. Rizzo, P. Cescutti, N. Ravenscroft

9:40 131. Cryopreservation of primary hepatocytes using oligosaccharides. **Y. Miyamoto**, S. Enosawa

10:00 132. An array-based method to identify high affinity inhibitors for carbohydrate-binding proteins. **Y. Zhang**

10:20 Intermission.

10:40 133. Analysis of protein glycation using phenylboronate acrylamide gel electrophoresis. M. P. Pereira Morais, J. D. Mackay, **T. D. James**, J. S. Fossey, J. M. van den Elsen

11:00 134. Redesigning the biological activities of heparan sulfate on a microfluidic chip. **J. G. Martin**, Y. Xu, W. Gressick, Z. Zhang, W. Zhao, R. Bhisetti, P. Paul, F. Zhang, J. Liu, J. S. Dordick, R. J. Linhardt

11:20 135. Detecting multivalency effects with glycodendrimers on microarray chips. **R. J. Pieters**, H. M. Branderhorst, N. Parera Pera, R. Kooij, R. M. J. Liskamp, R. Ruijtenbeek

11:40 136 Structure and dynamics of sucrose in aqueous solution by computer experiments. **J. Xia**, D. Case

CARB 1

1,3,2-oxathiaphospholane ring opening approach to the synthesis of analogs of nucleoside 5'-*O*-polyphosphates

*Damian Blaziak, Piotr Guga, Agata Jagiello, Anna Nowicka, Aleksandra Pietkiewicz, and **Wojciech J Stec**, wjstec@bio.cbmm.lodz.pl, Dept. Bioorganic Chemistry, Centre of Molecular & Macromolecular Studies, Polish Academy of Sciences, Sienkiewicza 112, Lodz 90-362, Poland*

The first P-stereocontrolled chemical synthesis of oligo(deoxyribonucleoside 3',5'-phosphorothioate)s (1) has been reported from this laboratory. P-Diastereomers of deoxyribonucleoside- 3'-O-(2-thiono-1,3,2 –oxathiaphospholanes) (2) under treatment with 5'-OH-nucleosides in the presence of strong organic bases such as DBU provide with satisfactory yield dideoxyribonucleoside -3',5'-phosphorothioates with full stereospecificity. The use of solid phase synthesis allows for preparation of mixed sequences of hexadecamers 1 with an average coupling yield of 96% (trityl assay)1. Here we demonstrate that chimeric PO/PS oligonucleotides with a predetermined sense of P-chirality can be obtained by combined phosphoramidite/oxathiaphospholane approaches due to application of a new oxidizing reagent. Otherwise, P-diastereomers of nucleoside- 5'-O-[2-thiono(seleno)-1,3,2 –oxathiaphospholanes] (3), have been found as satisfactory substrates for the synthesis of analogs of nucleoside-5'-O-polyphosphates, such as NDP- and NTP-α-S(Se) under treatment with phosphoric acid or inorganic pyrophosphate, respectively. Reaction of 3 with methylene-*bis*-phosphonate allows for preparation of an analogues of NTP-α-(S/Se) (4) with a methylene bridge replacing oxygen spanning Pβ and Pγ phosphorus atoms. The most intriguing results were obtained in DBU-assisted reaction of 3 with O,O-dialkyl H-phosphonates providing , upon stepwise removal of protecting groups , nucleoside 5'-O-α-thio-hypophosphate (5). Similarly, reaction of 3 with O,O-dialkyl H-phosphonothioates results in preparation of nucleoside-5'-O-Pα-Pβ-dithiohypophosphates (6), so far unknown analogues of NDP. New method of direct P-P bond formation has to be emphasized. Studies upon substrate activity of compounds 5 and 6 towards enzymes involved in metabolism of nucleoside 5'-O-polyphosphates are in progress.

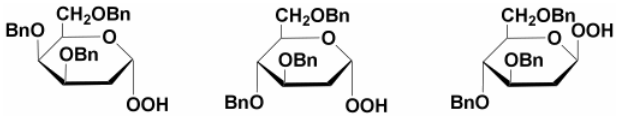
1. P.Guga, A.Okruszek, W.J.Stec: Recent Advances in Stereocontrolled Synthesis of P-Chiral Analogues of Biophosphates. In: *Topics in Current Chemistry*. Vol. 220, Springer Verlag Berlin Heidelberg **2002**, J.P.Majoral, Ed., pp. 169-200.

CARB 2

Anomeric hydroperoxides: Synthesis, enantioselective epoxidation

***Marek C. Chmielewski**, chmiel@icho.edu.pl, Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224, Warsaw, Poland, Fax: +48-22-632-66-81*

Oxidation of readily available 2-deoxysugars with 50 % hydrogen peroxide in the presence of sulfuric acid provides the corresponding hydroperoxides in 48-85 % yields. They are relatively stable and can be separated into pure anomers by chromatography. Hydroperoxides derived from 2-deoxy-galactose practically exist as single α-anomers only and can be used for enantioselective epoxidation without purification. Anomeric hydroperoxides derived from 3,4,6-tri-O-benzyl-galactose and glucose were used for enantioselective epoxidation of α,β-unsaturated carbonyl compounds. In the presence of sodium hydroxide epoxidations of en-ones showed exceptional high asymmetric induction up to ee = 95%. The exchange of sodium by potassium ion resulted in a low asymmetric induction. These result pointed to the crucial role of counterion and strongly suggested the coordination of the alkaline ion in the transition state of the epoxidation process by both reagents, hydroperoxide and the olefin. The theoretical studies of the reaction mechanism at the DFT (Density Functional Theory) B3LYP/6-31G* level explained well experimental facts.



CARB 3

Natural thio-sugars and their bioisosteres functionalizations

***Zbigniew J. Witczak**, zbigniew.witczak@wilkes.edu, Dept.of Pharmaceutical Sciences, Wilkes University, School of Pharmacy, Wilkes-Barre, PA 18766, Fax: 570-408-7828*

Natural thio-sugars employ unique mechanisms to mediate biologically and medically important recognition events. Given the diverse modes by which natural thio-sugars are recognized, a major challenge is to understand thio-saccharide function and to develop methods to inhibit or augment it. Thio-sugars constitute a new lead in the development of carbohydrate therapeutics as new potential anticancer and anti HIV agents. As the new concept of incorporating the sulfur linkage into an S-di, S-tri- and S-oligosaccharide analogs and sulfur as heteroatom progresses, the validity of the synthetic approaches and their stereoselectivity play a critical role in their synthesis. Our stereoselective approach to specific class of S-linked thio-sugars was first developed in 1995 and continue with new classes of specific RNA polymerase inhibitors such as natural tagetitoxin. The second target is thiolactomycin as a reversible inhibitor of the â-ketoacylsynthase (KAS) of bacterial fatty acid synthase (FAS and FAS II).

Both thio-derivatives serve key regulatory functions and are excellent possible targets for drug design.

Our new concept of incorporating peptide link into nonhydrolyzable thio-sugars moiety at different positions leads us to the development of the lead compound ZJW-713. The thio-carbo peptide (ZJW-713) and its new functional bioisosteres are being tested as potential agents to inhibit HIV-induced cell killing and virus production in CEM or MT-2 cells.

This presentation will summarize recent developments in the biological and chemical functionalization of bioisosteres of new analogs of thiolactomycin and tagetitoxin and thioanhydro-sugars, thio-disaccharides, from three major families. Progress toward the design and discovery of RNA polymerase and KAS specific inhibitors will be discussed as well.

CARB 4

Glycals: Conformational models and versatile synthons for anthracycline glycosides

***Derek Horton**, carbchm@american.edu, Chemistry Department, American University, 4400 Massachusetts Avenue, NW, Washington, DC 20016, Fax: 202-885-1095*

During more than a decade in the carbohydrate laboratories at Ohio State University, the drive, persistence, and experimental skills of Waldemar Priebe played a key role in the elaboration of a wide range of analogues of the classic antitumor antibiotics daunorubicin and doxorubicin. Most notably, coupling of the sugar component to the anthracycline aglycon via oxyhalogenation of a glycal precursor gave access to a series of related structures and allowed systematic optimization for greater antitumor activity and lower toxicity. It was shown that use of a chiral precursor glycal permits resolution of racemic synthetic analogues of the anthracycline aglycon. The glycals adopt half-chair conformations and, according to their substitution mode, may display unexpected conformational behavior

CARB 5

Galectins and their role in high-grade glioma tumor progression

***Charles Conrad**[1], cconrad8@comcast.net, Timothy Madden[2], Xiaoyang Sheng[2], and Waldemar Priebe[1], wp@wt.net. (1) Departments of Neuro-Oncology and Department of Experimental Therapeutics, The University of Texas, M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, (2) The*

University of Texas, M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030

Galectins are a family of carbohydrate-binding proteins with affinity for beta-galactoside, an epitope found on glycoproteins or glycolipids. Galectins have been found to be up-regulated in many tumors; in particular, Galectin-1, 3 and 7 appear to be more highly expressed in glial neoplasms. Galectins appear to be involved in many critical functions including, cell cycle progression, motility, invasion, avoidance of apoptosis and avoidance of immune surveillance. We previously demonstrated a correlation with patient survival times and Galectin-1 expression. Additionally, we demonstrated that stable transfection of U87 MG glioma cells with Gal-1 results in a 50% decrease in cell doubling time, whereas treatment of U87 MG cells with siRNA to Galectin-1 significantly reduced both motility and invasion in Matragel assays. Additionally, treatment of U87 MG cells with wt p53 results in export of galectin-1 to the extracellular space via exosomes. Protein profiling was performed on exosomes harvested from ~2 x107 U87 MG cells treated with wt p53 or empty vector. The proteomic investigation was performed by one-dimensional electrophoresis and nano-liquid chromatography tandem mass spectrometry of tryptic digests of the protein bands, followed by database searches. We identified >300 proteins from several functional categories in the exosomes, including proteins not previously reported with exosomal location in other studies. Structural proteins, chaperones, signal transduction proteins, MHC class I and II proteins, and enzymes related to glycolysis were also identified. Gal-1 and fifty-two other proteins, including CD97, CD109, CD166 (ALCAM), niban and kynureninase, were uniquely identified in exosomes derived from wt p53-treated cells. The identification of differentially expressed exosomal proteins (including Galectin-1) provides important clues about the role of exosomes in cellular crosstalk. Disaccahride sugars are being designed to inhibit Galectin-1 and Galectin-3 for the development of new sugar-based anti-tumor drugs. These issues will be discussed including the development of these sugar-based inhibitors.

CARB 6

Drug discovery in academia: A chemist in the biologist's cookie jar

***Waldemar Priebe**, Department of Experimental Therapeutics, University of Texas, M.D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030, Fax: (713)-665-4802*

The discovery of novel anticancer drugs in an academic environment will be presented and discussed from a chemist's perspective. Specifically, a novel approach to the design and development of small molecule drugs targeting DNA, the exploitation of carbohydrate metabolism, and the discovery of potent inhibitors of the Jak2/STAT3 pathway will be addressed. I will focus, in greater

detail, on the road from discovery to clinical development of Berubicin in brain tumors. Development of effective chemotherapeutic strategies to treat brain tumors has been limited, in part, by the inaccessibility of the CNS to pharmacological intervention. Topoisomerase II (topo II) overexpression is well documented in human gliomas and correlated to poor survival, but, to date, no effective topo II poison has been developed that is capable of reaching the target tissue after systemic administration. Berubicin is the first blood-brain barrier-penetrating topoisomerase II inhibitor with high activity against glioblastoma multiforme.

CARB 7

Caulobacter crescentus growth in xylan and cellobiose: Effect on microbial plant polysaccharide metabolism

Gopal R Periyannan*, grperiyannan@eiu.edu, Brant Riegel, and Dilani Gamage, Department of Chemistry, Eastern Illinois University, 600 Lincoln Avenue, Charleston, IL 61920*

Increasing global demand for oil has led to the investigation of alternative fuel sources. One such source is plant-derived polysaccharides biomass for bioethanol and other fuel molecule production. Decomposition of polysaccharide is a key step in generating bioethanol and can be carried out by microbial enzymatic conversion methods. The oligotrophic bacterium Caulobacter crescentus possesses genes for the total metabolism of different types of structural plant polysaccharides leading to its remarkable survivability in extremely nutrient-depleted conditions. In an effort to identify glycoside hydrolases produced by C. crescentus, we tested growth in sole carbon sources of xylan and cellobiose and analyzed the carbohydrate decomposition using GC/MS. The results clearly demonstrate the survivability of C. crescentus these carbohydrate media and the ability to deconstruction and utilize these carbohydrates. Generation of many carbohydrate derivative in the media indicate complex environmental carbohydrate metabolic pathways and efficient nutrient uptake systems must be present. This study will contribute to the basic knowledge of microbial polysaccharide metabolism and will yield information on new microbial enzymes, polysaccharide conversion methods and biomass derived materials for non-food based biofuel production.

CARB 8

Simulation of force spectroscopy for polysaccharides with a replica-exchange method enhanced umbrella sampling approach

Xiancheng Zeng[1]*, xiancheng.zeng@duke.edu, Hao Hu*[2]*, Huan-Xiang Zhou*[3]*, zhou@sb.fsu.edu, Piotr Marszalek*[4]*, pemar@duke.edu, and Weitao Yang*[1]*. (1) Department of Chemistry, Duke University, Durham, NC 27708, (2) Department of Chemistry, Duke University, (3) Department of Physics and Institute of Molecular Biophysics and School of Computational Science, Florida State University, Tallahassee, FL 32306, (4) Department of Mechanical Engineering and Materials Science, Duke University, 144 Hudson Hall, Edmund T. Pratt Jr. School of Engineering, Durham, NC 27708*

A replica-exchange method enhanced umbrella sampling (REM-US) approach combined with the weighted histogram analysis method (WHAM) was developed to simulate the force spectroscopy of polysaccharides under the tension exerted by the atomic force microscope (AFM). Compared with conventional steered molecular dynamics (SMD), the REM-US/WHAM approach significantly enhanced the convergence and efficiency of the sampling in the conformational space of polysaccharides. We have performed simulations for both stretching and relaxing processes of pustulan, a (1→6)-beta-D-Glucan, and the new approach generated identical force-extension curves for different pathways, which has not been possible with the conventional SMD approach. Moreover, the simulated force-extension curves are in good agreement with AFM measurements. In addition, the parallel efficiency of REM-US is much higher than SMD, since simulations with different extensions and different temperatures can be carried out simultaneously without heavy communication. The REM-US/WHAM approach provides an efficient and robust way to simulate force spectroscopy of polysaccharides under external mechanical tensions.

CARB 9

Understanding the polysaccharide chain in ionic liquid: A molecular dynamics study

Hanbin Liu*, hliu2@lbl.gov, Seema Singh, seesing@sandia.gov, Brad Holmes, bmholmes@lbl.gov, and Blake A Simmons, basimmons@lbl.gov, Joint BioEnergy Institute and Sandia National Laboratories, Livermore, Emeryville, CA 94608*

Pretreatment is one of the most costly steps in lignocellulosic biofuel production. Ionic liquids (ILs) are currently under intense study as solvents or additives for macromolecules and have been used in the pretreatment procedure of biomass. Some ionic liquids have been shown to be very effective solvent in solvating cellulose and some biomass types. There is no clear rationale to date in terms of selecting ionic liquids a priori for enhanced solubilization of these biopolymers. In this work, we performed molecular dynamic simulations with an all atom force field to investigate behavior of the polysaccharide chain placed in different solvents. A series of poly-glucose chains with increasing degrees of

polymerization were modeled in ionic liquids, water, organic polar solvent and binary systems. Thermodynamic properties such as density and solubility parameters are also calculated from simulations. The two-body solute-solvent interaction energy terms are calculated. We observed that the interaction energy between polysaccharide chain and IL is stronger than water and organic solvent. The conformations of polysaccharide chains in different solvent and their relationship with the degree of polymerization were also studied. This work will help inform the design and selection of ionic liquids and other solvents with enhanced solubilization characteristics.

CARB 10

Gum arabic-chitosan composite biopolymer scaffolds for bone tissue engineering

***Roberto A. Silva**, 90silva@cua.edu, Biomedical Engineering Department, The Catholic University of America, 620 Michigan Ave., N.E, Pangborn Hall 117, Washington, DC, DC 20064*

Biopolymer composites are a very promising area for developing novel tissue engineering (TE) scaffolds. Chitosan is known to have a variety of properties that make it suitable for TE applications due to its biocompatible, antibacterial, and biodegradable nature. Gum Arabic (GA) is a natural biopolymer that is incorporated into a number of food products. This study reports a biopolymer composite synthesized by mixing GA with Chitosan in amounts ranging from 0-90 wt% GA. The addition of GA caused a marked increase in the weight gain due to water uptake that the composite films exhibited. 100% chitosan films gained approximately 50 wt% on aging in water while 17 wt% chitosan-83 wt% GA films gained over 250 wt% due to water absorption. MC3T3-E1 mouse pre-osteoblast cells were used in an initial assessment of the suitability of these scaffolds for bone tissue engineering. Scanning electron microscopy (SEM) analysis was used as a method to characterize the films in vitro. The cells initially adhered to the composite films and exhibited minimal toxicity, but gradually started to detach from the films after one week.

CARB 11

Preparation and characterization of poly(lactic acid)/chitosan copolymers

***Ana C Fonseca**, anafs3@eq.uc.pt, Pedro N Simões, and Maria H Gil, Chemical Engineering Department, University of Coimbra, Rua Sílvio Lima-PóloII, Coimbra 3030-790, Portugal, Fax: 00351239798703*

This work deals with the synthesis and characterization of new poly(lactic acid) (PLA) / chitosan copolymers, with potential application in the biomedical field. The copolymers will gather in the same entity the better properties of both materials, leading to a new material with enhanced physico-chemical properties and biodegradability.

Chitosan was copolymerized with both hydroxyl- and carboxyl-terminated telechelic PLA oligomers. The telechelic PLA oligomers were obtained in a melt polycondensation reaction, using ethylene glycol and adipic acid as comonomers. The preparation of the copolymers was carried out in solution and different feed molar ratios oligomer/chitosan were used. The synthesized materials were characterized by NMR and FTIR spectroscopies and their thermal behavior was accessed by DMTA, DSC and TGA. Their swelling capacity and hydrolytic degradation behavior were also evaluated.

CARB 12

Controlled grafting modification of chitosan via living radical polymerization

***Jorge F. J Coelho**, jcoelho@eq.uc.pt, Department of Chemical Engineering, University of Coimbra, Polo II - Rua Silvio Lima, Coimbra 3030-790, Portugal, Fax: +351 239798703, and MH Gil, hgil@eq.uc.pt, Depatment of Chemical Engineering, University of Coimbra, Polo II, Rua Silvio Lima, Coimbra 3030-790*

This work deals with controlled grafting modification of chitosan via degenerative chain transfer and metal catalyzed living radical methods. The results indicate that the graft copolymers were successfully synthesized and that the grafting polymerization was a first-order reaction with respect to monomer concentration. The graft copolymers were characterized by NMR, FTIR, mDSC, GPC and DMA. This enables a wide variety of macromolecular designs to afford novel types of tailored made materials composed of a natural polysaccharides and synthetic polymers.

CARB 13

Influence of steaming time on steam explosion pretreatment of Lespedeza stalks (Lespedeza crytobotrya): Characteristics of degraded cellulose

*Kun Wang, Institute of Biomass Chemistry and Technology, Beijing Forestry University, 35 Qinghua East Road, Beijing 100083, China, Jianxin Jiang, Institute of Biomass Chemistry and Technology, Beijing Forestry University, Beijing 100083, China, **Feng Xu**, xfx315@163.com, College of Material Science and Technology, Beijing Forestry University, Qihun Road 35, beijing 100083, China,*

*Fax: 86-10-62336972, and **RunCang Sun**, Institute of Biomass Chemistry and Technology, Beijing Forestry University, QingHua East Road 35, Beijing 100083, China, Fax: 86-10-62336972*

The synergistic effect of steam-explosion pretreatment and sodium hydroxide post-treatment of Lespedeza stalks (Lespedeza crytobotrya) has been investigated in this study. In this case, Lespedeza stalks were firstly exploded at a fixed steam pressure (22.5kg/m2) for 2-10 min. Then the steam exploded Lespedeza stalks was extracted with 1 M NaOH at 50°C for 3 h with a shrub to water ratio of 1:20 (g/ml), which yielded 57.3, 53.1, 55.4, 52.8, 53.2, and 56.4% (% dry weight) cellulose rich fractions, comparing to 68.0% from non-steam exploded material. The content of glucose in cellulose residues increased with increment of the steaming time and reached to 94.10% at the most severity. The similar increasing trend occurred during the dissolution of hemicelluloses. It is evident that at shorter steam explosion time, autohydrolysis mainly occurred on the hemicelluloses and the amorphous area of cellulose. The crystalline region of cellulose was depolymerized under a prolonged incubation time. The characteristics of the cellulose rich fractions in terms of FT-IR, CP/MAS 13C NMR spectroscopy and thermal analysis were discussed, and the surface structure was also investigated by SEM.

Keywords: Lespedeza crytobotrya; Steam explosion; Steaming time; Fractionation; Cellulose

CARB 14

Preparation and properties of sodium carboxymethyl cellulose-hyaluronic acid-carboxymethyl chitosan blend films

***Xihong Zhao**, xhzhao2006@gmail.com, College of Light Industry and Food Sciences, South China University of Technology, Wushan Street, Guangzhou 510641, China, Xiaowei He, davidxwhe@126.com, Carbohydrate Lab, College of Light Industry & Food Science, South China University of Technology, Wu Shan, Guangzhou 510640, China, and Liansheng Yang, lflsyang@scut.edu.cn, College of Light Industry & Food Science, South China University of Technology, wushan road, Guangzhou 510640, China*

The Sodium Carboxymethyl Cellulose-Hyaluronic Acid-Carboxymethyl Chitosan blend films were prepared by solution method, and then characterized by FT-IR,XRD,SEM, percent water absorption, measurement of mechanical properties, degradation characteristic by PBS solution and enzyme.The results suggested that there were hydrogen bonding interaction and good compatibility in the blend films.The chemical degradation and biodegradation experiments proved that the degradation speed was decreased effectively and played the role of the local barrier material in the required time when the content of CMC was

75%,mHA:mCMCS=1:2 with cross-linking by 0.8%EDC.The blend films are expected to be used as controllable degradation biomaterials in the field of postsurgiery hemostasis and anti-adhesion.

CARB 15

Endoglycosidase-catalyzed transglycosylation: Mechanistic studies and synthetic applications

***Lai-Xi Wang**, LWang3@ihv.umaryland.edu, Department of Biochemistry and Moelcular Biology, University of Maryland School of Medicine, 725 West Lombard St, Baltimore, MD 21201*

The family 85 endo-beta-N-acetylglucosaminidase (ENGase) is a class of endoglycosidase that possesses both hydrolysis activity and transglycosylation activity. We have previously reported that the use of synthetic sugar oxazoline, the mimic of the presumed transition state, as the donor substrate not only expended the substrate availability, but also led to a dramatic enhancement of the transglycosylation yield. Our recent studies on substrate structural requirement have revealed a relaxed substrate specificity of the enzymatic transglycosylation, implicating a great potential of the enzyme for synthesis. On the other hand, site-directed mutagenesis of the ENGase (Endo-A and Endo-M) has led to the discovery of a new class of glycosynthase that is able to catalyze block transfer of oligosaccharide but lacks product hydrolysis activity. The use of the ENGase for the synthesis of glycoproteins, glycosylated small-molecule natural products, and novel polysaccharides will be discussed.

CARB 16

Carbohydrate-based drug discovery

***Chi-Huey Wong**, chwong@gate.sinica.edu.tw, Academia Sinica, 128 Academia Road, Section 2, Nankang District, Taipei 115, Taiwan, Fax: 886 2 2785 3852*

Protein glycosylation is the most complex post-translational process; more than 90 percent of human proteins are glycosylated. The significance of glycosylation at the molecular level is however not well understood, and as such the pace for the development of carbohydrate-based drug discovery and diagnosis is relatively slow. It is thus important to develop new tools to study the effect of glycosylation on the structure and function of proteins and other biologically active molecules. This lecture will focus on the development of new methods for the synthesis of homogenious glycoproteins with well defined glycan structure, glycoarrays for the high-throughput analysis of protein-glycan interaction and design of click-induced fluorescent probes for use to identify new cancer

biomarkers for diagnosis and drug discovery. New glycoprotein vaccines have been designed and developed to tackle the problems of flu and breast cancer.

CARB 17

Magnetic glyco-nanoparticles, a useful tool for detection and differentiation of bacteria and cancer cells

***Xuefei Huang**, xuefei@chemistry.msu.edu, Kheireddine El-boubbou, and Medha N. Kamat, kmedha@gmail.com, Department of Chemistry, Michigan State University, East Lansing, MI 48824*

Carbohydrates are ubiquitous in nature, which are often involved in molecular and cellular recognition. For example, many pathogens use mammalian cell surface carbohydrates as anchors for attachments and cancer cells can metastasize through carbohydrate and protein interactions. To utilize these effects for bio-sensing, we immobilized carbohydrates onto magnetic nanoparticles. The resulting magnetic glyco-nanoparticles (MGNP) bestow much higher avidities with lectins due to the multi-valency effect. The MGNPs were found to be very useful to rapidly detect bacterium such as Escherichia coli (E. coli) with just five minute incubation time. Up to 88% of an E. coli strain can be efficiently removed through MGNP binding. The responses patterns of several E. coli strains to the MGNPs allowed us to easily decipher the pathogen identity. This approach was further extended to study of cancer cells. The binding of cancer cells with MGNPs caused a reduction of T2 relaxation time, which was readily detected by Magnetic Resonance Imaging. It was discovered that cancer cells displayed drastically different affinities with a panel of MGNPs, allowing easy differentiation of these cell types. The high affinity MGNPs were also found to possess anti-adhesive properties against the cancer cells.

CARB 18

Mechanistic studies of C-4 deoxygenation in the biosynthesis of desosamine

***Hung-wen Liu**, h.w.liu@mail.utexas.edu, Division of Medicinal Chemistry College of Pharmacy and Department of Chemistry and Biochemistry, University of Texas, Austin, PHAR-MED CHEM PHR 4.220, 1 University Station, A1935, Austin, TX 78712-0128, Fax: 512-471-2746*

Desosamine found in a number of macrolide antibiotics, including methymycin and pikromycin produced by Streptomyces venezuelae, plays an essential role in conferring biological activities to its parent aglycones. The proteins encoded by the desI and desII genes in the methymycin/pikromycin biosynthetic gene cluster

have been proposed to catalyze C-4 deoxygenation in desosamine biosynthesis. Biochemical characterization showed that DesI is a PMP-dependent enzyme and DesII is a member of the radical S-adenosylmethionine (SAM) enzyme family. To study the catalytic properties of these two enzymes, both genes were expressed and the DesI and DesII proteins were purified to nearly homogeneity, The function and mechanism of these enzymes have been investigated. The progress of our study on the C-4 deoxygenation in the biosynthesis of desosamine will be presented.

CARB 19

Formation of C-C bonds via catalytic hydrogenation: Construction of carbohydrates and polyketides

Michael J Krische*, mkrische@mail.utexas.edu, Department of Chemistry and Biochemistry, University of Texas at Austin, Mail Code A5300, Austin, TX 78712*

Highly enantioselective carbonyl allylation, crotylation and reverse prenylation are achieved under transfer hydrogenation conditions employing an ortho-cyclometallated iridium C,O-benzoate catalyst. Using these methods, a known bryostatin A ring fragment is prepared in less than half the number of steps previously reported. Under the conditions of rhodium catalyze hydrogenation, acetylene reductively couples to aldehydes and imines. Catalyst-directed diastereoselective reductive coupling of acetylene to glyceraldehyde is used to prepare all eight L-hexoses.

CARB 20

De novo synthesis in carbohydrate chemistry

George A. O'Doherty*, George.ODoherty@mail.wvu.edu, Department of Chemistry, West Virginia University, Morgantown, WV 26506, Fax: 304-293-4904*

My research group has been working in two related areas of organic synthesis: carbohydrate synthesis and natural product synthesis. The unifying theme that connects our research in these two areas is our method of synthesis (asymmetric catalysis) and target selection (biological activity). A recurring theme in the group's synthetic approaches to both types of targets is our reliance on asymmetric catalysis for the control of asymmetry. Fundamental to our approach is the development of highly efficient routes that transform, via catalysis, inexpensive achiral starting materials into enantiopure products, which are poised for the conversion into complex molecules with biologically relevant properties (i.e., enantioselective synthesis of a new “chiral pool” via asymmetric catalysis). The ultimate goal of these synthetic projects is to develop

enantioselective routes to these complex molecules in sufficient quantities that are amenable for biomedical investigations. Examples of our approach are outlined in the below scheme.

CARB 21

Conjugate vaccines from synthetic carbohydrate antigens

***Pavol Pavol Kováč**, kpn@helix.nih.gov, NIDDK, LBC, Section on Carbohydrates, National Institutes of Health, 8 Center Drive, Bethesda, MD 20892-0815*

Our strategy for developing conjugate vaccines for bacterial diseases is based on the use of synthetic fragments of O-specific polysaccharides of bacterial pathogens as antigenic components. We synthesize oligosaccharides that mimic structure of the O-specific polysaccharides of bacterial pathogens and attach them chemically to protein carriers. Conjugation is essential because carbohydrates are poor immunogens. Multiple injections of neoglycoconjugates can sharply boost antibody titers and widen the spectrum of antibodies produced. Currently, we work, among other things, on developing conjugate vaccines for cholera and anthrax.

Cholera is an infectious, enteric, life threatening disease caused by some strains of Vibrio cholerae. We have made most significant progress in the development of a vaccine for cholera from the hexasaccharide mimic of the O-PS of Vibrio cholerae O:1, serotype Ogawa. Anthrax has not done much harm in the civilized world, but new concerns regarding anthrax have recently emerged in connection with the use of some form of Bacillus anthracis as a biological weapon. Our work towards a conjugate vaccine for anthrax is based on the use of the synthetic tetrasaccharide that is a side chain of the major glycoprotein of the Bacillus anthracis exosporium as an antigenic component of the vaccine.

For conjugation of synthetic carbohydrates to proteins we prefer the squaric acid chemistry. It is experimentally simple and very efficient, namely a large excess of the precious synthetic oligosaccharide is not required. The conjugation can be conveniently monitored by surface-enhanced laser desorption-ionization time-of-flight mass spectrometry (SELDI-TOF MS), which provides information about the progress of the conjugation in near-real time, similar to thin-layer chromatography in syntheses of small organic molecules. We will show that combination of the two methods allowed preparation of tailor-made neoglycoconjugates with predetermined carbohydrate-protein ratio.

CARB 22

GPI anchors: WHY and HOW the complex molecules are being synthesized

***Andrei V. Nikolaev**, a.v.nikolaev@dundee.ac.uk, College of Life Sciences, University of Dundee, Dundee DD1 5EH, United Kingdom, Fax: +44-1382-386373*

Glycosylphosphatidylinositols (GPIs) are a class of natural glycosylphospholipids that anchor proteins, glycoproteins and lipophosphoglycans to the membrane of eukaryotic cells. In parasitic protozoa, the GPIs are anchoring mucins and phosphoglycans, thus forming a dense protective layer (glycocalyx) on the surface of the parasites. This type of anchor appears to be present in these organisms with a much higher frequency than in higher eukaryotes. The function of GPI anchors has been extensively discussed and there is evidence, that GPIs and/or their metabolites can act as secondary messengers, modulating biological events including insulin production, insulin-mediated signal transduction, cellular proliferation and cell-cell recognition. The parasitic GPI structures are diverse and the scope of their functions, from host cell invasion to the deception of the host's immune system, is astonishing. All of those make the chemical preparation of the compounds and their analogues of great interest. The lecture will discuss the most recent synthetic approaches to the complex molecules.

CARB 23

Synthesis of anthrax dissacharides: Application toward an anthrax detection system

***Hua Yu Wang**, hwang9@mix.wvu.edu, Haibing Guo, haibingguojj@yahoo.com, and George A. O'Doherty, George.ODoherty@mail.wvu.edu, Department of Chemistry, West Virginia University, Morgantown, WV 26506*

A highly efficient and enantioselective route for the construction of the disaccharides portion of Anthrax has been established. The synthetic strategy feature the use of Pd mediated glycosylation, Luche reduction, and Upjohn dihydroxylation to securely install the desired stereochemistry of the natural á-L-á-L-dirhamnose and its unnatural á-L-á-D-dirhamnose diastereomer.

CARB 24

Half of sugar chemistry resides at the anomeric carbon

***Stephen Hanessian**, stephen.hanessian@umontreal.ca, Department of Chemistry, University of Montreal, 2800 Edouard Montpetit, Montreal, QC H3C3J7, Canada, Fax: 514-343-5728*

The anomeric carbon of a sugar molecule is endowed with special properties that distinguish it from other carbon atoms in the same molecule. In addition to its historic significance dating back to Emil Fischer, it brings together aspects of reactivity, stereolectronics, and biological relevance, all encompassed in the venerable glycosidic linkage. Stereocontrolled glycoside synthesis still remains as an ongoing major challenge. In spite of some significant advances in the area, a universally successful protocol as is often encountered in peptide coupling for example is still an elusive goal.

Efforts in the stereocontrolled design of glycosyl transfer reactions with applications to the synthesis of biologically relevant oligosaccharides and other glycosides will be presented.

CARB 25

Development of novel one-pot carbohydrate synthesis methodologies

***Xuefei Huang**, xuefei@chemistry.msu.edu, Department of Chemistry, Michigan State University, East Lansing, MI 48824*

Many innovative methods have been developed to facilitate oligosaccharide synthesis in recent years. Preferential activation of an armed donor in the presence of a disarmed one is the foundation of the highly successful reactivity based one-pot synthesis strategy. However, to prepare building blocks with desired anomeric reactivities, extensive protective group manipulations must be carried out, thus lowering overall synthetic efficiency. To solve this problem, a new pre-activation based one-pot glycosylation approach is developed for efficient assembly of oligosaccharides independent of anomeric reactivities. This is achieved by pre-activating the glycosyl donor, followed by sequential addition of building blocks in the same reaction flask. Synthesis of several complex oligosaccharides by this method will be discussed. Moreover, the results from mechanistic studies will be presented. The pre-activation based one-pot method represents an important advance towards streamlining oligosaccharide synthesis, which can potentially evolve into a general glycosylation approach complementing the current automated solid-phase technology.

CARB 26

Novel sugar-based heterocycles via the addition of aromatic imines to glycals

***Cecilia H. Marzabadi**, marzabce@shu.edu, Peter Dobbelaar, dobbelpe@shu.edu, Katherine Konchalski, and Kyle N. Brogden, Department of*

Chemistry and Biochemistry, Seton Hall University, 400 South Orange Avenue, South Orange, NJ 07079, Fax: 973-761-9772

The Povarov Reaction using benzaniline derivatives and endo- and exo- glycals was investigated to prepare a series of carbohydrate-based dihydroquinolines and quinolines. The results of catalyst optimization studies, as well as, mechanistic insights into the reaction, will be described. A one pot procedure for the direct preparation of quinolines will also be discussed.

CARB 27

New schemes in oligosaccharide synthesis

Nikolay N. Nifantiev*, nen@ioc.ac.ru, Nadezhda E. Ustyuzhanina, nadezhda.ustyuzhanina@gmail.com, Yury E. Tsvetkov, tsvetkov@ioc.ac.ru, Bozhena S. Komarova, kbozhena@gmail.com, Vadim B. Krylov, vadimkrilov@yandex.ru, Yuri V. Mironov, mironov-yuri@yandex.ru, and Alexey G. Gerbst, alger@ioc.ac.ru, Laboratory of Glycoconjugate Chemistry, N.D. Zelinsky Institute of Organic Chemistry Russian Academy of Sciences, Leninsky prospect 47, Moscow 119991, Russia, Fax: 007-499-1358784*

In this paper we will summarize our investigations on two main topics. First is the selective α-glycosylation by L-fuco-, D-gluco- and D-xylopyranosyl donors with the use of remote stereocontrolling participation of equatorial 3-O-acyl group in the donor with the formation of stabilized glycosyl cation intermediate whose nucleophilic attack is favored from α-side to give preferentially corresponding α-glycosides. Second topic is dedicated to the synthesis and stereoselective α- and β-glycosylation by 2-azido-2-deoxy-selenoglycosides. Practical applicability of described glycosylation methods is exemplified by the straightforward syntheses of complex oligosaccharides including selectively sulfated large fucoidan fragments, pentasaccharide glycoform of the outer core region of the *Pseudomonas aeruginosa* lipopolysaccharide, and α-linked xylosyl oligosaccharides from the blood-clotting factors.

This work was supported by Russian Academy of Sciences (Program 1, Division of Chemistry and Material Sciences) and Russian Foundation for Basic Research (grant 07-03-00225).

CARB 28

Chemoenzymatic synthesis of heparin and heparin oligosaccharides

Robert J. Linhardt*, linhar@rpi.edu, Department of Chemistry and Chemical Biology, Department of Chemical and Biological Engineering, Department of*

Biology, Rensselaer Polytechnic Institute, Troy, NY 12180, Jian Liu, liuj@email.unc.edu, Division of Medicinal Chemistry and Natural Products, University of North Carolina, Chapel Hil, NC 27599, Jonathan S Dordick, dordick@rpi.edu, Dept. of Chemical & Biological Engineering, Rensselaer Polytechnic Institute, Troy, NY 12180, and Shaker Mousa, mousas@acp.edu, Pharmaceutical Research Institute, Albany College of Pharmacy, Albany, NY, Albany, NY 12208

Heparin is a polysaccharide that exhibits numerous biological functions and is an important clinical anticoagulant prepared from porcine intestines. Recently, heparin produced in China and adulterated with a fully sulfated chondroitin polysaccharide was used in the US, resulting in a number of serious adverse reactions, including death. A non-animal source of heparin could help to reduce the inherent variability of this drug and improve the regulatory control of its manufacture. A new chemoenzymatic approach is under development that offers a route to the non-animal sourced, bioengineered heparin polysaccharide and heparin oligosaccharides. Progress on this effort will be discussed.

CARB 29

Oligosaccharide synthesis for glycobiology

***Yukishige Ito**, yukito@riken.jp, Synthetic Cellular Chemistry Laboratory, RIKEN Advanced Science Institute, 2-1 Hirosawa, Wako 351-0198, Japan, Fax: 48-462-4680*

Glycoproteins are characterized by their complexity and diversity. To clarify their functions, synthetic approaches are considered promising. Development of synthetic methodologies useful for efficient and facile preparation of oligosaccharides is a focal issue in carbohydrate chemistry. In light of their structural diversity, practical strategy to facilitate the synthesis of oligosaccharide is expected to be highly valuable.

We have developed methodologies for syntheses of several types of glycoprotein glycans. For instance, a systematic strategy to synthesize glycoprotein glycans that play important roles in glycoprotein quality control, was established. With structurally defined glycans and in hand, analyses of various enzymes, lectins, and chaperones, which are involved in glycoprotein processing and folding, were conducted, in order to reveal their specificities in a quantitative manner. Our research strategy has relied heavily upon key transformations developed by Per Garegg (thioglycosides as glycosyl donors) and Nikolay Kochetkov (conversion synthesis of glycosylamines).

CARB 30

Synthesis of carbohydrates linked to heterocyclic compounds

***El Sayed H. El Ashry**, eelashry60@hotmail.com, Department of Chemistry, Alexandria University, Faculty of Science, Alhoria Str, Alexandria, Egypt, Fax: 00203-4271360*

The conversion of carbohydrates to heterocycles has been known since a long time.1This approach could provide functionalized heterocycles which have industrial or biological values. We have studied the synthesis and reactions of a number of glycosyl-sulfanyl heterocycles. Variety of five and six-membered heterocyclic compounds was used. The conventional and the microwave assisted their synthesis will be presented.

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CARB 31

Synthesis of oligosialic acids

***Takashi Takahashi**, ttak@apc.titech.ac.jp, Department of Applied Chemistry, Tokyo Institute of Technology, 2-12-1-S-135 Ookayama, Meguro 152-8552, Japan, Fax: +81-3-5734-2884*

Sialic acids are a family of the most complex monosaccharide units in naturally occurring oligosaccharides, and are frequently located at the non-reducing ends of oligosaccharides. Recent progress in glycobiology suggests that α(2,8) and α(2,9) di/oligo and polysialic acids may play important roles in biological events that occur on the cell surface. However, the synthesis of α linked sialic acid derivatives represents one of the most difficult and challenging processes in the chemical synthesis of oligosaccharides. Herein we present the synthesis of α(2,9) and α(2,8) oligosialic acids using 5-N,4-O-carbonyl protected thiosialosides. The donors underwent α-sialylation without need for use of acetonitrile. In addition, combinatorial synthesis of ganglio-sireses of ganglioside epitoes is also reported.

CARB 32

Thioglycosides as glycosyl donors: Synthesis of complex microbial carbohydrate structures

***Stefan Oscarson**, stefan.oscarson@ucd.ie, Centre for Synthesis and Chemical Biology, University College Dublin, Belfield, Dublin 4, Ireland, Fax: +353 17162501*

The finding and development, starting in the mid-eighties, of efficient thiophilic promoters have made thioglycosides very attractive as glycosyl donors, especially in convergent synthesis approaches. Their stability during protecting group manipulations and orthogonal glycosylation reactions combined with their effective chemoselective activation facilitates the formation of large stable but still reactive building blocks. The use of thioglycosides in the synthesis of a number of complex microbial structures will be exemplified, structures needed for development of efficient glycoconjugate vaccines. Synthesis of structures corresponding to capsular polysaccharide structures from the bacteria Streptococcus pneumoniae type 14, Vibrio cholerae type O-139, and the fungi Cryptococcus neoformans type A and D will be presented as well as synthesis of lipopolysaccharide core structures from the bacteria Haemophilus influenzae, Neisseria menigitidis and Moraxella catarrhalis.

CARB 33

Synthetic oligosaccharides as vaccine candidates for microbes classified as bioterrorism agents

***Geert-Jan Boons**, gjboons@ccrc.uga.edu, Department of Chemistry, Complex Carbohydrate Research Center, University of Georgia, 315 Riverbend Road, Athens, GA 30602*

Capsular polysaccharides (CPS) and lipopolysaccharides (LPS) are major components of the cell surface of bacteria. These components are important virulence factors by impeding phagocytosis, promoting bacterial colonization and persistence on mucosal surfaces and by interfering with leukocyte migration and adhesion. With a few exceptions, bacterial polysaccharides can induce an adaptive immune response and not surprisingly, they have been employed for the development of vaccines against several pathogens.

Oligosaccharides isolated from microbes are often heterogeneous, which makes it difficult to obtain well-defined fragments. Furthermore, LPS and CPS may contain fragments that suppress the immune response or induce auto-immune reactions. Selective removal of these unwanted domains is often very difficult. Chemical conditions required for the conjugation of a polysaccharide to a carrier protein may lead to the destruction of vital immuno-dominant components. Fortunately, these problems can be addressed by using synthetic oligosaccharide epitopes. Synthetic components can be equipped with an artificial spacer for controlled coupling to a carrier protein. A range of synthetic oligosaccharides can be used to determine the minimal epitope for a protective

antibody response. Synthetic oligosaccharides can also be employed for mapping of the ligand requirements of monoclonal antibodies raised against natural polysaccharides. Antibodies raised against well-defined synthetic oligosaccharides may be used to determine which epitopes are expressed during the life cycle of a pathogen.

We have devised efficient synthetic protocols for oligosaccharides derived from Bacillus anthracis, Francisella tularensis and Burkholdaria pseudomallei. These pathogens are classified as bio-terrorism agents and their polysaccharides are vaccine and diagnostic candidates. Therefore, the compounds have been coupled to carrier proteins and the resulting conjugates examined for immune responses.

CARB 34

RNA targeting by siRNAs for therapeutics

Muthiah Manoharan*, mmanoharan@alnylam.com, Department of Drug Discovery, Alnylam Pharmaceuticals Inc, 300 Third Street, Cambridge, MA 02142*

RNA interference (RNAi) is a powerful biological process for specific silencing of mRNAs in diversified eukaryotic cells. By introducing chemical modifications into synthetic siRNA building blocks, desirable "drug-like" properties can be imparted to the siRNAs. siRNAs containing chemical modifications show enhanced resistance towards nuclease degradation, less immune stimulation, and reduced "off-target" effects compared to unmodified siRNAs. To achieve in vivo delivery, certain chemical conjugates and novel formulations are being investigated. A summary of this progress will be presented.

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2. Akinc, A.; et al. “A combinatorial library of lipid-like materials for delivery of RNAi therapeutics.” Nature Biotech. 2008, 26, 561-569.

3. Wolfrum, C.; et al. “Mechanisms and optimization of in vivo delivery of lipophilic siRNAs.” Nature Biotech. 2007, 25, 1149-1157.

4. Krutzfeldt, J.; et al. “Specificity, duplex degradation and subcellular localization of antagomirs.” Nucleic Acids Research 2007, 35, 2885-2892.

5. Bumcrot, D.; et al. “RNAi therapeutics: a potential new class of pharmaceutical drugs.” Nature Chemical Biology 2006, 2, 711-719.

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7. Manoharan, M. “RNA interference and chemically modified small interfering RNAs.” Curr. Opin. Chem. Biol. 2004, 8, 570-579.

8. Soutschek, J.; et al. “Therapeutic silencing of an endogenous gene by systemic administration of modified siRNAs.” Nature 2004, 432, 173-178

CARB 35

Crystallographic analyses and structure/activity correlations of siRNA modifications

***Martin Egli**, martin.egli@vanderbilt.edu, Department of Biochemistry, Vanderbilt University, School of Medicine, 607 Light Hall, Nashville, TN 37232, Fax: 615-322-7122*

Chemical modification of nucleic acids can have profound effects on thermodynamic and chemical stability, function and activity. We are studying chemically modified nucleic acids (CNAs) in the contexts of their structure and activity as antisense oligonucleotides (AONs) and small interfering RNAs (siRNAs), an etiology of nucleic acid structure, and the origins of substrate recognition by DNA- and RNA-processing enzymes. Using recent examples of crystal structure determinations of RNAs with 2'-modifications, the talk will summarize insights gained from structure into key properties for therapeutic applications, including target affinity, nuclease resistance and in vitro and in vivo activity.

CARB 36

Novel and structurally biased backbone modifications of nucleic acids

***Vaijayanti A. Kumar**, va.kumar@ncl.res.in, Division of Organic Chemistry, National Chemical Laboratory, Pune 411008, India*

Intensive research in the last couple of decades has developed oligonucleotides as leads for antisense (AS) drug development. The principle of AS drugs, based on the direct utility of sequence information and sequence specific recognition of nucleic acids using Watson-Crick base-pairing, practically encompasses potential treatment for several diseases ranging from viral and bacterial infections to cancerous, inflammatory or genetic disorders. Complete replacement of sugar-phosphate backbone by achiral, acyclic and uncharged scaffold in aminoethylglycyl peptide nucleic acids (aegPNA) has been extensively studied in

the last two decades. We present our research efforts to develop structurally biased ON analogues and dephosphosphono backbone in DNA. Some of our recent important results showcasing the structural analogues of DNA that bind strongly and sequence specifically to the target mRNA will be presented.

CARB 37

PNA analogs with potential for selective RNA targeting

***Krishna N Ganesh**, Indian Institute of Science Education and Research, 900, NCL Innovation Park, Dr Homi Bhabha Road, Pune 411008, India*

Peptide nucleic acids have established a pre-eminent position as nucleic acid analogs with high specificity and affinity of binding complementary DNA and RNA sequences. The limitations for their successful application have been their poor cell permeability and almost equal affinity for isosequential complementary DNA and RNA.WE have been addressing ways to overcome these disabilities by pre-organization of PNA conformation through various chemical modifications for selective binding of DNA or RNA and not both. This is feasible since DNA:PNA and RNA:PNA duplexes hace dufferent geometric structures and conformational requirements for PNA. Our earlier approaches involved cyclic, chiral analogues and we are now simplifying this by use of achiral, acyclic, sterically constrained modifications. This presentation describes our recent approaches and their potentials along with attempts to develop inherently cationic PNAs for better cell permeability.

CARB 38

Multivalent binding oligomers to target TAR

***Daniel H. Appella**, Laboratory of Bioorganic Chemistry, NIDDK, DHHS, National Institutes of Health, 9000 Rockville Pike, Bethesda, MD 20892*

We are investigating a class of molecules termed multivalent binding oligomers (MBOs) to target folded RNA structures. These molecules are derived from polypeptides in which the peptide backbone amide groups are replaced by amino linkages. We envisioned that the non-ionic side chains of an MBO can afford hydrogen bonding or aromatic-aromatic stacking to RNA base pairs, while the backbone amines interact with the anionic RNA backbone. MBOs were designed to target the transactivation response element (TAR), a critical RNA in regulating transcriptional elongation of the HIV genome. Our results show that the lead MBOs inhibit tat-TAR association at low micromolar concentration and with good specificity. Studies using cell-based assays demonstrate that the lead MBOs are cell permeable, have low toxicity, and inhibit the tat-TAR association in the

assay. Antiviral activity in HIV-infected peripheral blood mononuclear cells will also be presented.

CARB 39

Synthesis and characterization of new siRNA prodrugs

Richard Johnsson[1]*, richard.johnsson@mail.mcgill.ca, Jeremy G. Lackey*[1]*, jeremy.lackey@mail.mcgill.ca, and Masad J. Damha*[2]*, masad.damha@mcgill.ca. (1) Department of Chemistry, McGill University, 3420 University Street, Montreal, QC H3A 2A7, Canada, (2) Department of Chemistry, McGill University, 801 Sherbrooke Street West, Montreal, QC H3A2K6, Canada*

Small interfering RNAs (siRNA) are large (~ 12 kD), highly charged molecules (~ 40 negative charges) and thus do not readily cross the cell membrane. siRNAs also activate the immune response and are rapidly degraded in the body by endogenous enzymes. Many groups have focused on different ways to circumvent these problems and for example, it has been shown that covalently attachment of a cholesterol molecule to the terminus of siRNA greatly increase cellular permeability.

In our lab, we have been developing siRNA prodrugs to enhance cellular uptake and increase chemical stability. The idea is to synthesize siRNA with bio-labile lipophilic groups that will enhance cell membrane permeability. Once inside the cell, endogenous enzymes should cleave the lipophilic groups, releasing active siRNA.

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CARB 40

Efficient GeRP-mediated oral delivery of siRNA to macrophages modulates inflammation in mice

Myriam Aouadi, Gregory J Tesz, Sarah M Nicoloro, My Chouinard, Mengxi Wang, Ernesto Soto, Michael P Czech, and ***Gary Ostroff****, Program in Molecular Medicine, University of Massachusetts Medical School, 373 Plantation Street, Biotech 2, Suite 113, Worcester, MA 01604*

RNA interference (RNAi) shows great therapeutic promise to selectively regulate gene expression. However, the efficient delivery of dsRNA molecules (siRNA) to specific cells to affect RNAi remains a challenge. To accomplish targeted oral delivery of siRNA to macrophages we have developed a new delivery technology based on the synthesis of Glucan encapsulated siRNA Particles(GeRPs). We have recently reported that a mitogen-activated protein kinase (Map4K4) controls TNFα signaling in macrophages (Nature, in press). Orally treating mice with Map4K4 GeRPs delivering 20µg siRNA/Kg effectively knocked down both Map4K4 and TNFα mRNA levels in murine peritoneal exudate cells, and splenic and liver macrophages compared to PBS and scrambled siRNA controls. Treatment with Map4K4 GeRPs provided significant protection against an LD_{90} challenge of LPS-Galactosamine by inhibiting TNFα production. These results demonstrate efficient *in vivo* oral GeRP-mediated delivery of siRNA, and the potential utility of targeting macrophage gene expression by RNAi to modulate inflammatory diseases.

CARB 41

Modified regions of bacterial ribosomes as target sites for new ligands

Christine S. Chow, *csc@chem.wayne.edu, Chemistry, Wayne State University, 5101 Cass Ave., Detroit, MI 48202, Fax: 313-577-8822*

The synthesis of modified nucleosides and corresponding phosphoramidites allows for the generation of modified RNAs representing various regions of bacterial ribosomes. Availability of the phosphoramidites allows for the synthesis of hairpin or duplex RNA analogues containing the natural modifications at specific locations. RNAs representing the 970-loop region (helix 31) and the decoding region (helix 44) of 16S rRNA and helix 69 of 23S rRNA were synthesized with and without the natural modifications. Subsequently, different constructs with singly and fully modified RNAs were examined and compared with the unmodified RNAs for stability, structure, and conformational changes. Peptide ligands for these different modified rRNA regions were identified by using M13 phage display with a seven-amino-acid library. The relative affinities and selectivities of the peptides for the modified rRNA targets and ribosomes were determined by using a variety of biophysical methods.

CARB 42

Helix-threading ligands for targeting RNA

Peter A Beal, *beal@chem.ucdavis.edu, Department of Chemistry, University of California, Davis, One Shields Avenue, Davis, CA 95616*

Controlling RNA function with low molecular weight ligands is a challenging and important goal. Organic small molecules tend to have more favorable uptake and distribution properties than oligonucleotide-based RNA targeting agents. However, creating RNA-binding small molecules with the requisite affinity and specificity remains a daunting task. Nevertheless, recent advances in our understanding of small molecule-binding riboswitch regulators of gene expression underscore the validity of this approach. The Beal group has investigated the use of short helix-threading peptides as a recognition motif for binding sites found in duplex RNAs. These molecules have a heterocyclic structure (e.g. quinoline) inserted into the peptide backbone allowing them to bind certain double helical RNA structures by threading intercalation. Here we describe their synthesis as well as binding affinity and selectivity for various RNA targets, including to a site found in human pre-miRNA.

CARB 43

Exploring RNA recognition processes using fluorescent nucleosides

***Yitzhak Tor**, Department of Chemistry and Biochemistry, University of California, San Diego, La Jolla, CA 92093*

RNA molecules play key roles in essential biological processes and are evolving as important targets for therapeutic intervention. Ligands which specifically bind unique RNA sites and prevent the formation of key RNA folds or RNA–protein complexes can modulate cell functions and are likely to be of therapeutic potential. To learn about such recognition events and to fabricate discovery assays, one needs to advance effective biophysical tools. When carefully designed and implemented, fluorescent nucleosides, nucleotides and oligonucleotides can serve an unparalleled role in such studies. The lecture will describe our program, aiming at the design and development of new emissive isomorphic nucleoside analogs. The motivation for this work will be outlined by introducing RNA–ligand interactions. The design and synthesis of fluorescent isosteric nucleobase analogs and their utilization for the fabrication of "real-time" fluorescence-based biophysical assays will then be presented.

CARB 44

Targeting the hepatitis C virus internal ribosome entry site RNA

***Thomas Hermann**, tch@ucsd.edu, Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093, Fax: 858 534 0202*

The internal ribosome entry site (IRES) is a highly conserved structured element of the hepatitis C virus (HCV) genomic RNA and therefore provides an attractive target for antiviral drugs. We have investigated the mechanism of action of an inhibitor of the HCV subgenomic replicon. It is demonstrated that selective conformational induction at a structured domain of the IRES is responsible for the inhibition of viral translation in cells infected with HCV

CARB 45

Targeting RNA with aminosugars

Dev P. Arya*, dparya@clemson.edu and Nihar Ranjan, Department of Chemistry, Clemson University, H. L , Huner Laboratories, Clemson, SC 29634, Fax: 864 656 6613*

Aminosugars have been used to target various RNA structures. Previous work from our lab has shown the ability of small molecule and oligonucleotide based conjugates to target RNA sequence-specifically. Recent progress in our efforts to develop RNA specific conjugates will be presented.

CARB 46

A dynamic combinatorial approach to the challenge of sequence-selective RNA recognition

Benjamin L. Miller*, benjamin_miller@urmc.rochester.edu, Center for Future Health and Department of Dermatology, University of Rochester School of Medicine and Dentistry, 601 Elmwood Avenue, Box 697, Rochester, NY 14642, Fax: 585-273-1346*

The development of peptide, small-molecule, or hybrid structures able to sequence-selectively recognize RNA constitutes a significant, unsolved fundamental challenge for bio-organic chemistry. We have employed a library selection process, termed “Resin-Bound Dynamic Combinatorial Chemistry”, or RBDCC, for the identification of peptide/small molecule hybrid RNA-binding compounds. This method has allowed us to obtain lead compounds for an RNA stemloop critical for HIV replication, and for (CUG) repeat RNA, believed to be the causative agent of type I myotonic dystrophy. Recent efforts to further improve compound affinity and selectivity, and replacement of peptidic portions of the molecules with peptidomimetics, will be discussed.

CARB 47

Using an RNA motif-ligand database to help rationally target RNA with small molecules

***Matthew D. Disney**, mddisney@buffalo.edu, Department of Chemistry, Center for Excellence in Bioinformatics & Life Sciences and Department of Chemistry, University at Buffalo, State University of New York at Buffalo, Buffalo, NY 14260, Fax: 716-645-6963*

RNA is an important potential target for therapeutic and chemical genetic probe development. However, most of this potential is untapped. We hypothesize that this is mainly due to the limited information available on the types of RNA motifs that are targets for small molecules. Herein, we disclose the use of Two-Dimensional Combinatorial Screening (2DCS) to establish a database of the RNA motifs that small molecules bind and describe using this database to facilitate the rational and modular design of small molecules targeting the RNA.

CARB 48

Biophysical characterization and conformational analysis of antiproliferative factor (APF): A novel anticancer lead compound

***Kristie M. Adams**[1], adamskm@mail.nih.gov, Piotr Kaczmarek[2], pkaczmarek@ncifcrf.gov, Yi-Chien Lee[1], leey@ncifcrf.gov, Susan K Keay[3], skeay@medicine.umaryland.edu, and Joseph J. Barchi Jr.[4], barchi@helix.nih.gov. (1) Laboratory of Medicinal Chemistry, National Cancer Institute at Frederick, 376 Boyles Street, Building 376 Room 117, Frederick, MD 21702, Fax: 301-846-6033, (2) Medicinal Chemistry, National Cancer Institute at Frederick, 376 Boyles Street, Bldg 376 Rm 218, Frederick, MD 21702, (3) Infectious Diseases, University of Maryland School of Medicine, 10 N Greene Street, Baltimore VA Medical Center, Room 3B-184, Baltimore, MD 21201, (4) Laboratory of Medicinal Chemistry, National Cancer Institute at Frederick, NIH, 376 Boyles Street, Bldg 376, Room 209, Frederick, MD 21702*

Interstitial cystitis (IC) is a chronic bladder disease affecting an estimated 1.3 million Americans, mostly women. IC is characterized by recurring pain and discomfort in the bladder and the surrounding pelvic region, resulting from thinning and/or ulceration of the bladder epithelial lining. Antiproliferative factor (APF), a negative growth factor isolated from the urine of IC patients, inhibited normal bladder epithelial cell growth at subnanomolar concentrations. APF also inhibited proliferation in a number of human cancer cell lines, leading to the hypothesis that APF could function as a novel anticancer drug. Structurally, APF is a nine-residue peptide containing sialyl-TF antigen α-O-linked to the N-terminal threonine residue of the peptide, Neu5Acα2-3Galβ1-3GalNAcα-O-TVPAAVVVA. Structure-activity relationship studies have revealed that small changes to the peptide sequence either greatly diminish or abolish activity. Biophysical

characterization and conformational analysis of APF and several APF analogues have been performed, and the results of these studies will be presented.

CARB 49

Biosynthetic production of N-linked glycans coupled with in vitro enzymatic processing to produce homogenous high mannose, hybrid, and complex type oligosaccharides

***Brian S. Hamilton**, bshamilt@indiana.edu, Interdisciplinary Biochemistry Graduate Program, Indiana University, 800 E. Kirkwood Ave., Bloomington, IN 47405-7102, Rui Chen, chenr@indiana.edu, Department of Chemistry, Indiana University, 800 E. Kirkwood Ave., Department of Chemistry, Bloomington, IN 47405-7102, Mark Pawlicki, Interdisciplinary Biochemistry Graduate Program, Indiana University, 800 E. Kirkwood Ave. Department of Chemistry, Bloomington, IN 47405-7102, and Thomas J Tolbert, tolbert@indiana.edu, Department of Chemistry, Indiana University, 800 E. Kirkwood Ave., Bloomington, IN 47405*

N-linked glycosylation has been found to be involved in numerous cellular processes that include cell-cell adhesion, cell growth, and immunity. However, study of the influence of N-linked glycosylation in biological systems is hindered due to the difficulty in isolation of appreciable yields of N-linked glycans. This difficulty in isolation of the amount of glycans suitable for biochemical study is mainly due to glycoprotein microheterogeneity. Glycoproteins produced in higher order eukaryotes contain a variety of glycoforms on a given protein, which causes great difficulty in isolation of particular glycoforms. Therefore, to obtain human N-linked oligosaccharides, a highly glycosylated protein was expressed in a glycosylation deficient yeast strain that produces human-like, high mannose N-linked glycans. Methods for the extraction of high mannose N-linked glycans from glycosylation deficient yeast, in vitro processing of glycans to produce hybrid and complex type N-linked glycans, and N-linked glycan isotopic labeling will be presented.

CARB 50

Carbohydrate separation through boron affinity saccharide electrophoresis

***John S Fossey**[1], J.S.Fossey@bham.ac.uk, Tony D. James[2], T.D.James@bath.ac.uk, Jean M van den Elsen[3], J.M.H.V.Elsen@bath.ac.uk, and Marta P Pereira Morais[3], M.P.Pereira.Morais@bath.ac.uk. (1) School of Chemistry, University of Birmingham, Edgbaston, Birmingham B15 2TT, United Kingdom, (2) Department of Chemistry, University of Bath, Claverton Down, Bath BA2 7AY, United Kingdom, (3) Department of Biology and Biochemistry, Univerity of Bath, Bath BA2 7AY, United Kingdom*

Boron is incorperated into polyacrylamide gels for electrophoresis. The inclusion of boron permits carbohydrates appended by a fluorophore to be separated where they otherwise could not be.

CARB 51

Interactions between transition metal particles and biopolymer chains modify the helical structure of amylose

***Paul Bernazzani**, paul.bernazzani@lamar.edu and Brian A. McKinley, Department of Chemistry & Physics, Lamar University, PO Box 10022, Beaumont, TX 77710*

One of the requirements of most enzyme-substrate systems is that the structure of the substrate must be such that it can fit in the binding pocket of the enzyme. Modifying the substrate structure will affect the enzyme's activity and be informative as to the binding requirements of the enzyme but also as to the structure of the substrate. Hence the enzymatic activity can be a probe of molecular structure modification. We investigated the effect of modifying the structure of amylose chains on the kinetics of enzymatic cleavage. The structural modifications involved interactions between the biopolymer chains and two types of transition metal particles: ZnSe, and TiO_2. The structural changes were followed using FTIR spectroscopy and differential scanning calorimetry (DSC) while the enzymatic activity was determined using the starch-iodine complexation method. Results show that interactions with ZnSe increase the rate of digestion while interactions with TiO_2 significantly slows down the reaction. Structural analysis suggests that strain variations in the backbone are the driving forces behind the experimental observations.

CARB 52

Glucosylation of raffinose via glucansucrase acceptor reactions

***Gregory L. Cote**, greg.cote@ars.usda.gov, Bioproducts and Biocatalysis Research Unit, USDA ARS NCAUR, 1815 N. University Street, Peoria, IL 61604, Fax: 309-681-6040, Christopher A. Dunlap, Crop Bioprotection Research Unit, USDA ARS NCAUR, 1815 N University St, Peoria 61604, and Karl E. Vermillion, New Crops and Processing Technology Research Unit, USDA ARS NCAUR, 1815 N University St, Peoria, IL 61604*

The trisaccharide raffinose (α-D-galactopyranosyl-(1→6)-α-D-glucopyranosyl-(1↔2)-β-D-fructofuranoside) occurs in the seeds of many plants, especially legumes, along with its galactosylated homologues stachyose and verbascose. The glucansucrase known as alternansucrase [EC 2.4.1.140] transfers glucosyl

units from sucrose to raffinose to give good yields of oligosaccharides which may serve as prebiotics. The main products were the tetrasaccharides α-D-glucopyranosyl-(1→3)-α-D-galactopyranosyl-(1→6)-α-D-glucopyranosyl-(1↔2)-β-D-fructofuranoside and α-D-glucopyranosyl-(1→4)-α-D-galactopyranosyl-(1→6)-α-D-glucopyranosyl-(1↔2)-β-D-fructofuranoside in ratios ranging from 4:1 to 9:1, along with lesser amounts of α-D-glucopyranosyl-(1→6)-α-D-galactopyranosyl-(1→6)-α-D-glucopyranosyl-(1↔2)-β-D-fructofuranoside. Ten unusual pentasaccharide structures were isolated. Three of these arose from glucosylation of the major tetrasaccharide product, two each from the minor tetrasaccharides, and three were the result of glucosylations of the fructose acceptor products leucrose or isomaltulose. The major pentasaccharide products arose from glucosylation of the major tetrasaccharides at position 4 of the fructofuranosyl unit. A number of hexasaccharides and higher oligosaccharides were also produced but their structures were not determined. The yields of oligosaccharides were much higher using alternansucrase than with dextransucrase [EC 2.4.1.5]. The main product of the dextransucrase-catalyzed glucosylation was α-D-glucopyranosyl-(1→4)-α-D-galactopyranosyl-(1→6)-α-D-glucopyranosyl-(1↔2)-β-D-fructofuranoside, which is at odds with the previously published structure.

CARB 53

Quantitative analysis of intact glycolipid-CD1d interaction

Pi-Hui Liang[1]*, phliang@ntu.edu.tw, Yung-Ling Lee*[2]*, Chih-Wei Fu*[3]*, and Ming-Han Hsieh*[3]*. (1) Institute of Pharmaceutical Sciences, National Taiwan University, College of Medicine, 1, Sec 1, Jen-Ai Road, Taipei 10018, Taiwan, Fax: 886-2-23225095, (2) Institute of preventive medicine, National Taiwan University, Taipei, Taiwan, (3) National Taiwan University*

The protein CD1d binds self and foreign glycolipids for presentation to CD1-restricted T cells by means of TCR recognition, and activates TH1 and TH2 chemokines release. In this study, a variety of glycolipid ligands were attached to a microarray or Biacore surface and their binding with CD1d investigated. An alpha-galactosyl ceramide (alpha-GalCer) bearing a carbamate group at the 6'-OH position was tethered to the surface and the dissociation constant with CD1d determined. Competition assays were used to determine the dissociation constants (Ki) of the glycolipids.

CARB 54

Structural and biochemical characterization of the fungal GPI transamidase

Yug Varma[1]*, yug@chem.wayne.edu, Megan Ehrenwerth*[2]*, mehrenw1@jhu.edu, and Jesse Klebba*[1]*. (1) Department of Chemistry, Wayne State University, 5101 Cass Ave, Detroit, MI 48202, (2) Department of Chemistry, Johns Hopkins University, 3400 N Charles St, Baltimore, MD 21218*

GPI anchoring is an essential eukaryotic post-translational modification that uses a glycosylphosphatidylinositol (GPI) anchor as an alternative mechanism to associate proteins with membranes. GPI transamidase (GPI-T) is a multi-subunit membrane bound ER enzyme that catalyzes the replacement of a C-terminal signal sequence in the protein substrate with the GPI anchor. GPI-T is comprised of five subunits - Gpi8, Gaa1, Gpi16, Gpi17 and Gab1. Each of these subunits is membrane associated and contains at least one transmembrane domain. Three of these subunits (Gpi8, Gaa1 and Gpi16) tightly associate with one another and copurify as a complex from yeast. While it is well established that Gpi8 contains the active site machinery for GPI-T, the precise roles of the other subunits remain less clear and largely speculative. To address this question, we have developed methods to express and purify the truncated soluble domains of Gpi8, Gaa1, and Gpi16, all from *Saccharomyces cerevisiae*. We have previously reported that $Gpi8_{23\text{-}306}$ forms a caspase-like homodimer. Here we show that the soluble domain of Gaa1, $Gaa1_{50\text{-}343}$ directly interacts with this $Gpi8_{23\text{-}306}$ homodimer. The results of experiments to characterize this Gpi8/Gaa1 complex will be presented.

CARB 55

Studies of heparin-protein interaction using click chemistry

Smritilekha Bera*, beras@rpi.edu, Department of Chemistry and Chemical Biology, Rensselaer Polytechnic Institute, 110 8th Street, Troy, NY 12180-359, Fax: 518-276-3405*

Heparin is a sulfated polysaccharide belonging to the family of glycosaminoglycans and widely used as an anticoagulant drug based on its ability to accelerate the rate at which antithrombin inhibits serine proteases in the blood coagulation cascade. Heparin has numerous important biological activities, associated with its interaction with diverse proteins. With the discovery of increasing numbers of heparin binding proteins there was a need to characterize the molecular properties, within the proteins and heparin, responsible for specific recognition. The aim of our recent project is to design UDP-sugars that are clickable to the fluorescence tagged compound, to synthesize heparin by elongation of a sugar chain and to detect the heparin-protein interaction.

CARB 56

ZnSe nanoparticles insertion modify the physical properties of starch-polyethylene blends

***Paul Bernazzani**, paul.bernazzani@lamar.edu and Durga P. Obulasetty, Department of Chemistry & Physics, Lamar University, PO Box 10022, Beaumont, TX 77710*

The development of an easily processable material based on starch has been impeded by the large amount of inter and intra-molecular bonds in starch. To overcome this problem, we investigate the effect of adding various amounts and types of nanoparticle to blends of polyethylene-starch. Results show that the addition of an intermediate amount of ZnSe particles resulted in a more flexible material with a modulus one order of magnitude lower that the blen without particles. FTIR scans suggest that the particles could disrupt the intramolecular bonds of starch. Addition of other types of nanoparticles of similar dimensions (10 nm) did not lead to a similar improvement of the physical properties of the material. Thermal analysis revealed that brittleness increased when the material was heated at 130^{o}C for more than 5 hours. Our results suggest that the ZnSe nanoparticles disrupt the stability of the biopolymer helices.

CARB 57

Clearing a path for nerve growth by the immobilized chondroitinase

***Zhongping Xiao Jr.**, xiaoz3@rpi.edu, Department of Chemistry, Rensselaer Polytechnic Institute, 110 8th St, Troy, NY 12180, and Robert J. Linhardt, Department of Chemistry, RPI, 110 8 th st, troy, NY 12180*

Severed nerve fibres in the spinal cord are hardly regenerated as they should go through a thicket of obstacles at the injury position. Previous study used a bacterial enzyme to prune these obstacles and the results from animal test showed optimistic future for researchers. However, it didn't led to complete recovery partially because of the short time of the half-life of the enzyme in vivo. In our study, we prolonged the half-life of enzyme by cross-linked it to silica nano particles and this immobilized enzyme showed better results than previous study. Hopefully, we can use the immobilized enzyme to prune back the extracellular-matrix shrubbery for the regenerated never fibres.

CARB 58

Synthesis of 13C labeled UDP-nucleotides for the enzymatic preparation of 13C labeled oligosaccharides

***Sayaka Masuko**, masuks@rpi.edu, Michel Weiwer, Jin Hwan Kim, and Robert J. Linhardt, Department of Chemistry and Chemical Biology, Rensselaer Polytechnic Institute, 110 8th Street, Troy, NY 12180*

Glycosaminoglycans (GAGs) are acidic, linear, heterogeneous polysaccharides present on the cell surface. GAGs regulate a wide range of physiological and pathophysiological functions through their interaction with a variety of different proteins. A better understanding of these interactions relies on the availability of well-defined, GAG oligosaccharides. Heparin, the most studied GAG, is extensively used in medical practice as an anticoagulant. Preparation of heparin can be achieved by synthetic and enzymatic methods using UDP-sugars as building blocks of the oligosaccharide. The preparation of 13C labeled heparin would be of great interest in order to study their molecular structures as well as their interactions with different proteins using 13C NMR. 13C labeled UDP-GlcA and UDP-GlcNTFA will be used to build 13C labeled heparin oligosaccharides for further protein interaction study.

CARB 59

Activity study on several mutants heparin lyase II

***Wenjing Zhao**, zhaow4@rpi.edu, Department of Biology, Rensselaer Polytechnic Institute, 110 8th Street, Troy, NY 12180, Zhenqing Zhang, zhangz5@rpi.edu, Department of Chemistry, RPI, 110 8 th st, troy, NY 12180, Zhongping Xiao, xiaoz3@rpi.edu, Chemistry and chemical biology, Rensselaer Polytechnic Institute, 110 8th Street, Troy 12180, Miroslaw Cygler, McGill University, Montreal, Canada, and Robert J. Linhardt, linhar@rpi.edu, Department of Chemistry and Chemical Biology, Department of Chemical and Biological Engineering, Department of Biology, Rensselaer Polytechnic Institute, Troy, NY 12180*

Activity assay of several mutants Heparin lyase II (HepII) has been done on both polysaccharide and structure-defined tetraoligosaccharides as substrate. Reaction products have gone through spectrophotometry, PAGE and LC/MS for subsequent analysis with regard to enzymetic conversion rate and specificity. Results give evidence and help elucidate the beta-elimination mechanism underlined the process of depolymerization based on their revealed crystal structure.

CARB 60

Studying galactosyltransferases that are important for the viability of *Mycobacterium tuberculosis*

Venkatachalam Raja Annamalai[1], *annamalai@chem.wisc.edu, John F. May*[2], *Rebecca Splain*[1], *splain@chem.wisc.edu, Christine Brotschi*[1], *and Laura L. Kiessling*[3], *kiessling@chem.wisc.edu. (1) Department of Chemistry, University of Wisconsin—Madison, 1101 University Ave, Madison, WI 53706, (2) Department of Biochemistry, University of Wisconsin—Madison, 433 Babcock Drive, Madison, WI 53706, (3) Departments of Chemistry and Biochemistry, University of Wisconsin—Madison, Madison, WI 53706*

The emergence of drug-resistant strains of *Mycobacterium tuberculosis*, the causative agent of tuberculosis, has impelled efforts to develop new targets for therapies. To this end, our research group has been investigating essential galactosyltransferases that incorporate galactofuranose residues into the mycobacterial cell wall. These enzymes act on lipid-linked oligosaccharide primers, which cannot be readily isolated from the bacteria. Synthetic routes that provide the means to access these critical substrates are needed. We have focused on this key objective and our recent results will be presented.

CARB 61

Analysis of isolated and purified *Staphylococcus aureus* capsular polysaccharide via monoclonal antibodies, mass spectrometry, and nuclear magnetic resonance spectroscopy

Ravonne Maxon[1], *rdmaxon@student.ysu.edu,* ***Joelle M. Wells***[1], *wellsjoelle@yahoo.com, Allen D. Hunter*[2], *adhunter@ysu.edu, Matthias Zeller*[2], *mzeller@cc.ysu.edu, and Dr. Diana Fagan*[3], *dlfagan@ysu.edu. (1) Department of Chemistry, Youngstown State University, 1 University Plaza, Youngstown, OH 44555, (2) Department of Chemistry, Youngstown State University, 1 University Plaza, Youngstown, OH 44555-3663, (3) Department of Biology, Youngstown State University, 1 University Plaza, Youngstown, OH 44555*

Staphylococcus aureus is an opportunistic bacterial pathogen responsible for causing a variety of human diseases including: foreign body infection, bacteremia, abscesses, and wound infections. Eleven antigenically distinct capsular polysaccharides, which have been shown to enhance virulence, are recognized for *Staphylococcus aureus*. Of these eleven, two types (type 5 and type 8) comprise about 70-95% of the isolates from patients with S. aureus disease. Type 5 and type 8 strains of *S. aureus* are isolated by killing the bacteria and removing DNA, RNA, and teichoic acid. The sample is then applied to a DEAE column followed by Sephacryl S-300 column for further purification. After each column the sample is tested for presence of carbohydrates (red tetrazolium test) and teichoic acid (phosphate test). Monoclonal antibodies specific for capsule are then used in an ELISA as a final step to identify purified the capsular polysaccharides. Samples can then be analyzed by nuclear magnetic resonance spectroscopy and mass spectrometry to confirm the structure of the capsule.

Confirmation of the capsule structure can then be used in the development of several types of treatments for *S. aureus*, by proving that antibodies are binding to the capsule and not a different molecule on the cell such as, teichoic acid.

CARB 62

Application of crosslinked rice starches as drug delivery matrices in monolithic tablets

*Christopher Peluso[1], **Fernanda O. Onofre**[1], fonofre@uark.edu, Guadalupe Mendez-Montealvo[1], mariam@uark.edu, and Ya-Jane Wang[2], yjwang@uark.edu. (1) Department of Food Science, University of Arkansas, 2650 N Young Ave, Fayetteville, AR 72704, Fax: 479-575-6936, (2) Department of Food Science, University of Arkansas, 2650 N. Young Ave., Fayetteville, AR 72704*

Waxy rice and regular rice starches were cross-linked with epichlorohydrin to 0.01, 0.05, and 0.1% levels and their sustained release properties and matrix rheological characteristics were evaluated. Cross-linking improved the sustained release properties of waxy rice starches, but did not have a significant impact on regular rice starch matrices. The proportion of amylose and amylopectin played an important role on the functionality of rice starch matrices. Cross-linking increased the swelling power of both starches, which may have contributed to the improvement of the sustained release properties of waxy rice starch. Rheological characterization of the swollen tablet matrices showed an increase in elasticity, organization, and stiffness of starch matrices upon cross-linking for both starch types. The modification of the microstructural characteristics by cross-linking improved the sustained release ability of waxy rice matrices, but had little impact on that of regular rice starch.

CARB 63

Disaccharide composition analysis of glycosaminoglycans from 4 human embryonic stem cells

***Boyangzi Li**[1], lib4@rpi.edu, Zhenqing Zhang[2], zhangz5@RPI.EDU, Alison V. Nairn[3], avnairn@uga.edu, Kelley W. Moremen[3], Stephen Dalton[4], sdalton@uga.edu, and Robert J Linhardt[1], linhar@rpi.edu. (1) Departments of Chemistry and Chemical Biology, Rensselaer Polytechnic Institute, Center for Biotechnology and Interdisciplinary Studies, 110 8th Street, Troy, NY 12180, (2) Department of Chemistry, Rensselaer Polytechnic Institute, Troy, NY 12180, (3) Complex Carbohydrate Research Center, University of Georgia, 315 Riverbend Road, Athens, GA 30602, (4) Department of Biochemistry and Molecular Biology, The University of Georgia, S245 Paul D. Coverdell Center, Athens, GA 30602*

Glycosaminoglycans (GAGs) play important role in binding with variable growth factors which control the process of cell differentiation and development. Previous study has suggested that the change both in the quantity and composition of GAGs are relevant to stem cell differentiation. However, most of those works were done using one specific type of stem cells. Little information about the GAG compositions among different cell lines was available. In our study, we investigate the composition of disaccharides extracted from undifferentiated hESCs of 4 frequently-used cell lines— BG01, BG02, H7 and H9. We compared the compositions of disaccharides of both the type of heparin/heparan sulfate (HP/HS) and of chondroitin sulfate/dermatan sulfate (CS/DS) from those cell lines. Also we used qRT-PCR to look at the transcription levels of enzymes involved in the biosynthesis of those GAGs in those 4 cell lines.

CARB 64

Expression and characterization of enzymes for bioenzymatic sythesis of heparin

Priscilla A. Paul*, paulp@rpi.edu, Chemical & Biological Engineering, Rensselaer Polytechnic Institute, 110 8th Street, Troy, NY 12180, Jonathan S Dordick, dordick@rpi.edu, Dept. of Chemical & Biological Engineering, Rensselaer Polytechnic Institute, Troy, NY 12180, Robert J. Linhardt, linhar@rpi.edu, Department of Chemistry and Chemical Biology, Department of Chemical and Biological Engineering, Department of Biology, Rensselaer Polytechnic Institute, Troy, NY 12180, Jian Liu, liuj@email.unc.edu, Division of Medicinal Chemistry and Natural Products, University of North Carolina, Chapel Hil, NC 27599, and Wenjing Zhao, zhaow4@rpi.edu, Department of Biology, Rensselaer Polytechnic Institute, 110 8th Street, Troy, NY 12180*

The goal of the Linhardt Lab and collaborators of the Bioengineering Research Partnership is to synthesize 1kg of non-animal source heparin by way of bioenzymatic synthesis. In the biosynthesis, N-sulfated heparosan, produced by E. coli K5 fermentation and subsequent N-deacetylation and sulfation, is modified by several O-sulfotransferases (OST) to produce heparin. 2-OST, 6-OST-1, and 3-OST-1 transfer sulfo groups from 3'-phosphoadenosine-5'-phosphosulfate (PAPS) to the positions 2-O- of uronic acid, and 6-O- and 3-O of the glucosamine. The expression and characterization of these necessary enzymes are critical to this process. OST have been expressed in E. coli and assayed for their activities including 2-OST, 3-OST-1, 6-OST-1, and 6-OST-3. Sulfotransferase activity was detected using a continuous spectrophotometric coupled-enzyme assay based on the regeneration of PAPS from desulfated 3'-phosphoadenosine-5'phosphate (PAP) by a recombinant aryl sulfotransferase using p-nitrophenyl sulfate as the sulfate donor and visible spectrophotometric indicator of enzyme turnover.

CARB 65

Glycoside library of plant steroids for immunological characterization

Maria Iacovidou[1]*, miacovid@hunter.cuny.edu, Akira Kawamura*[2]*, Zhitao Li*[3]*, and Kamlesh Sharma*[3]*. (1) Department of Chemistry and Biochemistry, Hunter College and The Graduate Center of the City University of New York, 695 Park Ave, New York, NY 10021, (2) Department of Chemistry and Biochemistry, Hunter College and The Graduate Center of the City University of New York, 695 Park Ave, New-York, NY 10021, (3) Department of Chemistry, Binghamton University, Binghamton, NY 13902*

Our group has previously identified four phytosteryl glucosides, including beta-sitosteryl-beta-D-glucoside, as immunostimulatory principles in an Oriental herbal formulation called Juzen-taiho-to (JTT). These plant steroids synergistically activate the nuclear factor kappa B (NF-kB) pathway in monocytes, a prototypical signaling pathway for immunostimulation, as evidenced by the induction of ICAM-1 mRNA. It is, however, not known if phytosterols with other sugars, such as galactose, xylose, etc., would also elicit immunological responses. In order to determine the structural requirements of the sugar moiety for immunostimulation, we have prepared a focused glycoside library of phytosterol. In this presentation, immunomodulatory activities of the synthesized compounds will be described.

CARB 66

Hydroxypropylated starches of varying amylose contents as sustained release matrices in monolithic tablets

Fernanda O. Onofre*, fonofre@uark.edu, Department of Food Science, University of Arkansas, 2650 N Young Ave, Fayetteville, AR 72704, Fax: 479-575-6936, and Ya-Jane Wang, yjwang@uark.edu, Department of Food Science, University of Arkansas, 2650 N. Young Ave., Fayetteville, AR 72704*

Waxy corn, common corn, and 70% high amylose corn starches were hydroxypropylated to two levels and their sustained release properties and matrix rheological characteristics were evaluated. The sustained release properties of common corn and high amylose corn starches were significantly improved with hydroxypropylation, and a higher level of hydroxypropylation resulted in better sustained release matrices. However, such improvements were not observed in waxy corn starch matrices, demonstrating that the performance of the matrix was dependent on the proportion of amylose and amylopectin in the starch. Hydroxypropylation markedly increased the swelling power of starches, which may have contributed to the improvement of the sustained release properties of amylose-containing starch. Rheological characterization of the swollen tablet

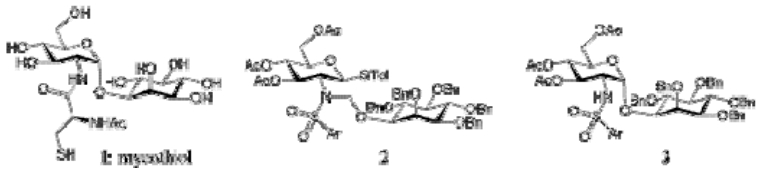
matrices showed an increase in fluidity and a decrease in elasticity and stiffness of starch matrices upon hydroxypropylation, particularly for amylose-containing starches, which may contribute to the improvement of the sustained release properties of starch tablets.

CARB 67

Intramolecular glucosamine alpha-glycosylation: Mycothiol

Kehinde Ajayi[1]*, kajayi@rutchem.rutgers.edu, Vinay Thakur*[2]*, Robert C. Lapo*[1]*, and Spencer Knapp*[3]*. (1) Department of Chemistry and Chemical Biology, Rutgers University, 610 Taylor Rd., Piscataway, NJ 08854, (2) Department of Chemistry and Chemical Biology, Rutgers University, 610 Taylor Road, Piscataway, NJ 08854-8087, (3) Department of Chemistry and Chemical Biology, Rutgers University, 610 Taylor Road, Piscataway, NJ 08854*

Synthetic studies on mycothiol (1) are described. The route features a unique intramolecular glycosylation of the methylene-tethered glucosamine derivative 2. Cyclization to give exclusively the alpha glycoside 3 occurs upon activation with (methylthio)dimethylsulfonium tetrafluoroborate (81%). The N-(arylsulfonyl) group (aryl = 2-naphthyl) is selectively removed by sodium amalgam (79%).



CARB 68

Labeling of lipoglycans with quantum dots

Maria Gonzalez-Moa*, MariaGonzalez@asu.edu, Carlos Morales Betanzos, and Sergei A. Svarovsky, Sergei.Svarovsky@asu.edu, Center for Innovations in Medicine, Biodesign Institute at ASU, 1001 S McAllister Ave, Tempe, AZ 85287*

Bacterial lipopolysaccharides (LPS), endotoxins, are the major constituents of the outer surface of Gram-negative bacteria, occupying up to 90% of the bacterial cell surface and being responsible for septic shock. The understanding of the mechanisms of LPS action and the developing of antisepsis drugs depends on the availability of efficient labeling strategies for LPS molecules. Ideally, such labeling should be non disruptive to the LPS functionality. Here, we report an application of hydrophobic quantum dots for non covalent labeling of LPS and its derivatives. This method takes advantage of the amphiphilic nature of lipoglycans

and does not introduce any chemical modalities to the LPS structure, making it ideally suitable for studying glycan interactions.

CARB 69

Multivalent presentation of tumor-associated carbohydrate antigen using gold nanoparticles as scaffold for immunotherapeutic applications

Raymond P Briñas[1]*, Andreas Sundgren*[1]*, Micah Maetani*[2]*, Kate Rittenhouse-Olson*[3]*, Padmini Sahoo*[3]*, Susan Morey*[3]*, Amy Houghton*[3]*, and Joseph J. Barchi Jr.*[1]*. (1) Laboratory of Medicinal Chemistry, National Cancer Institute at Frederick, 376 Boyles Street, Frederick, MD 21702, (2) Laboratory of Medicinal Chemistry, National Cancer Institute at Frederick, 376 Boyles Street, Bldg 376 Rm 209, Frederick, MD 21702, (3) Department of Clinical Laboratory Science, School of Health Related Professions, The State University of New York at Buffalo, Buffalo, NY 14214*

We have designed and synthesized gold nanoparticles (Au NPs) bearing multiple units of a tumor-associated carbohydrate, Thomsen-Friedenreich (TF) disaccharide in various forms. In one of these forms, the TF disaccharide was O-linked to either serine or threonine residues of a specific, thiol-functionalized 16-mer peptide repeating unit from a specific tumor-associated mucin (MUC4). The Au NPs were further functionalized with a segment from a form of the complement-derived protein, C3d and this hybrid construction was used as a novel vaccine platform. Au NPs consisting of various MUC4 glycopeptides interspersed with C3d and the linker used to attach them to the particle surface were synthesized and used to immunize mice. A moderate response was elicited when these AuNPs were injected subcutaneously over a period of 12 weeks. We present the optimization of the Au NP size, ligand structure, and the density of active ligands with respect to improving the observed immune response.

CARB 70

Nonhydrolyzable, lipid-linked inositol glycan with potential anticancer activity

Meenakshi Goel*, meenakshi_goel926@yahoo.com, Department of Chemistry, San Jose State University, One Washington Square, San Jose, CA 95192-0101, and Marc d'Alarcao, mdalarcao@science.sjsu.edu, Department of Chemistry, San José State University, One Washington Square, San José, CA 95192-0101*

Inositol glycans (IGs) are naturally occurring oligosaccharides that can stimulate insulin sensitive cells. Several synthetic IG analogues have been shown to activate the insulin-signaling pathway, including the stimulation of the enzyme

pyruvate dehydrogenase (PDH) phosphatase. Thus IGs can stimulate aerobic metabolism in cells. Cancer cells shift to anaerobic metabolism in order to escape intrinsic apoptosis (Warburg Effect). IG's ability to stimulate aerobic metabolism might provide a method to reverse the Warburg Effect and thereby induce apoptosis in the cancer cells. Indeed, **1** has recently been shown to *selectively* kill cancer cells while having no adverse effect on normal cells. However, **1** is unstable under physiological conditions due to ester hydrolysis and acyl group migration. In an effort to reduce this instability, we are preparing **2** and **3** in which the ester linkage is replaced by an ether or thioether moiety respectively. This poster reports on the progress towards the synthesis and biological evaluation of **2** and **3**.

CARB 71

Optimization of GeRP-mediated siRNA transfection

Shira Kahlon*, kahlon.shiro@umassmed.edu, Ernesto Soto, and Gary Ostroff, Program in Molecular Medicine, University of Massachusetts Medical School, 373 Plantation Street, Biotech 2, Suite 113, Worcester, MA 01604*

One of the most exciting advances in gene therapy in the last few years has come from the discovery of RNA interference allowing for precise gene-specific silencing of expression using double-stranded RNA (siRNA). We have previously reported on the use of glucan particles (GP) as a versatile macromolecular delivery technology to deliver DNA and proteins. Here we describe our current efforts to employ this technology to deliver siRNA in Glucan encapsulated siRNA Particles (GeRP) synthesized as a layer-by-layer polyplex with polyethyleneimine. To optimize the GeRP formulation we have screened polymeric and small molecule excipients for their effect on siRNA polyplex integrity and endosomal release using fluorescent siRNA binding and release, and an in vitro sequential GFP cotransfection system. These efforts have resulted in the development of a highly efficient siRNA delivery system requiring just 25 ng (1.8 pmol) of siRNA to silence GFP expression in 105 cells.

CARB 72

Probing the origin of diastereoface selectivity in a SmI2-mediated pinacol cyclization

***Kejia Ding**, dinotin@sbcglobal.net, Department of Chemistry, San Jose State University, One Washington Square, San Jose, CA 95192-0101, Alexander Kornienko, akornien@nmt.edu, Department of Chemistry, New Mexico Institute of Mining and Technology, 801 Leroy Place, Socorro, NM 87801, David I. Turner, Cubist Pharmaceuticals, 65 Hayden Avenue, Lexington, MA 95192-0101, and Marc d'Alarcao, mdalarcao@science.sjsu.edu, Department of Chemistry, San José State University, One Washington Square, San José, CA 95192-0101*

The synthesis of insulin-mimetic inositol glycan analogues requires the ready availability of differentially protected *myo*- and *chiro*-inositols. It has been previously demonstrated that these precursors can be efficiently prepared by SmI2-mediated intramolecular pinacol cyclization of xylose-derived dialdehydes. The stereoface selectivity of these reactions is highly dependent on the configuration of the aldehyde and the reaction conditions. In the case of pseudo-C_2-symmetric dialdehydes, the steroselelectivity changes dramatically depending on the temperature of the aqueous quench, implying a change in mechanism. We are engaged in a study to indentify the intermediates involved in the reaction pathways leading to these two different stereochemical outcomes. In this poster we report our progress toward understanding the features that control the diastereoface selectivity in this pinacol cyclization under each set of conditions.

CARB 73

Solution structure of a central fragment of the tumor antigen Le^aLe^x

***Mona Svensson**[1], Trudy A. Jackson[2], An Wang[2], Göran Widmalm[1], and France-Isabelle Auzanneau[2]. (1) Department of Organic Chemistry, Stockholm University, Arrheniuslaboratoriet, 106 91 Stockholm, Sweden, Fax: 0046-154908, (2) Department of Chemistry, University of Guelph, 50 Stone Road East, Guelph, Ontario N1G 2W1, Canada*

The trisaccharide β-D-Glc*p*NAc-(1→3)-β-D-Gal*p*-(1→4)-β-D-Glc*p*NAc-OMe is a central fragment of the Le^aLe^x hexasaccharide, which is commonly expressed by squamous lung carcinoma cells. Using the Le^aLe^x hexasaccharide as an antigen would likely induce an autoimmune reaction since the terminal non-reducing Le^a trisaccharide is commonly expressed by healthy tissue. However, some monoclonal antibodies raised against Le^aLe^x have been demonstrated to be specific for internal epitopes of the hexasaccharide while showing no cross-reactivity with Le^a. It is therefore of interest to identify and fully characterize such epitopes, thereby permitting the development of the necessary targeted vaccines. Here we interpret conformational information obtained for the above

trisaccharide, using the 2D J-HMBC experiment which gives information on trans-glycosidic $^{3}J_{C,H}$ and 1D $^{1}H,^{1}H$-NOESY experiments.

CARB 74

The stereoselective synthesis of C-linked neuraminic acid oligosaccharides

Jin-Hwan Kim[1]*, kimj16@rpi.edu, Sayaka Masuko*[1]*, Tyler Poore*[1]*, Smritilekha Bera*[1]*, beras@rpi.edu, and Robert J Linhardt*[2]*, linhar@rpi.edu. (1) Department of Chemistry and Chemical Biology, Rensselaer Polytechnic Institute, 110 8th Street, Troy, NY 12180-359, Fax: 518-276-3405, (2) Departments of Chemistry and Chemical Biology, Rensselaer Polytechnic Institute, Center for Biotechnology and Interdisciplinary Studies, 110 8th Street, Troy, NY 12180*

Polysialic acid (PSA), a long linear á(2-8)-linked polymer of sialic acid, is widely distributed in nature, from bacteria to humans. PSA is expressed on the meningitis-causing bacteria, Neisseria meningitidis B, and the capsular polysaccharide of Escherichia coli K1. It has also been found on the cell surface in a number of important cancers and is believed to be associated with metastasis and correlates with tumor progression. In this respect, PSAs are important targets for biological studies, in the development of vaccines for protection against meningococcal infection, and for the treatment of various cancers including Wilms' tumor and small cell lung carcinoma.

PSAs are known to exhibit both chemical and enzymatic hydrolytic instability. The PSA glycosidic linkages are very labile and subject to self-cleavage under mildly acidic conditions. In contrast, C-glycosides, in which the interglycosidic oxygen atoms are replaced with carbon atoms, are resistant to chemical and enzymatic degradation. The unusual lability of PSAs, their participation in developmental biology and their reappearance in various tumors, makes their C-glycosidic analogs ideal targets for a wide array of experimental, biological and potential therapeutic applications.

Herein, we report diastereoselective synthesis of C-linked á(2-8) oligosialic acids.

CARB 75

Synthesis of three-component cancer vaccines and immunotherapy studies in MUC1.tg mice

Pamela S. Thompson[1]*, pamelat@uga.edu, Vani Lakshminarayanan*[2]*, Therese Buskas*[3]*, tbuskas@ccrc.uga.edu, Sandra J. Gendler*[2]*, and Geert Jan Boons*[4]*, gjboons@ccrc.uga.edu. (1) Department of Chemistry, Complex Carbohydrate Research Center, University of Georgia, 315 Riverbend Rd., Athens, GA 30602,*

Fax: 706-542-4412, (2) Mayo Clinic Arizona, 13400 E Shea Boulevard, Scotsdale, AZ 85259, (3) Complex Carbohydrate Research Center, University of Georgia, 315 Riverbend Road, Athens, GA 30602, (4) Department of Chemistry, University of Georgia, Complex Carbohydrate Research Center, 315 Riverbend Road, Athens, GA 30602

The over-expression of oligosaccharides, such as Globo-H, Lewis^{Y}, and Tn antigens, is a common feature on tumor cells. Traditional cancer vaccine candidates composed of a tumor associated carbohydrate conjugated to a carrier protein (e.g. KLH, BSA) have failed to elicit sufficient titers of IgG antibodies. We have developed fully synthetic three-component vaccine candidates composed of a tumor-associated antigen, a promiscuous peptide T-helper epitope, and a lipopeptide adjuvant. In our first approach the compounds were synthesized by solid-phase peptide synthesis (SPPS) combined with native chemical ligation (NCL). Here, we compare our initial approach with microwave-assisted SPPS combined with microwave-assisted NCL. We have previously reported that the three-component vaccine induces strong immune responses in BALB/c mice as seen by high titers of MUC1 specific IgG antibodies. The vaccine candidates were evaluated for their abilities to eradicate tumor cells in both therapeutic and prophylactic tumor challenge studies. The results from these tumor challenge studies and the antibody and cytotoxic T-lymphocyte responses will be reported. Analogues of this three-component vaccine carrying STn and Tn_3 antigens are also being investigated.

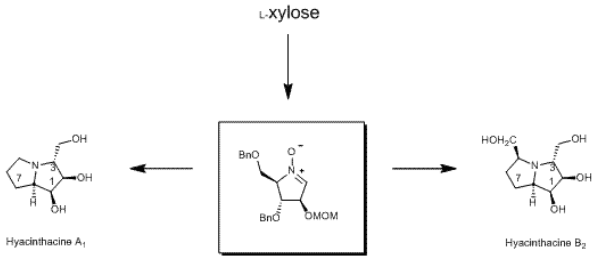
CARB 76

Synthesis of glycosidase-inhibiting bicyclic iminosugars

***Alan S. McComb**, A.S.McComb@hw.ac.uk, David R Adams, D.R.Adams@hw.ac.uk, and Richard H Wightman, School of Engineering and Physical Sciences, Heriot-Watt University, Riccarton, Edinburgh, EH14 4AS, United Kingdom*

Iminosugars are analogues of mono- or disaccharides where the ring oxygen is replaced by a nitrogen atom. It has been reported that iminosugars are inhibitors of glycosidases. Glycosidases play an important role in many biological processes. Therefore the use of iminosugars as glycosidase inhinitors has attracted much interest. This may have significance in the treatment of cancer, viral infections, diabetes and obesity. An intermediate nitrone was prepared, form L-xylose, with differential protection at O-3. Such a nitrone gives access, by routes involving 1,3-dipolar cycloaddition and subsequent stereochemical inversion at C-1, to the recently isolated Hyacinthacine class of pyrrolizidine alkaloids where the hydroxyl groups at C-1 and C-2 (hyacinthacine numbering system) are cis- to each other. This work leads to the synthesis of

Hyacinthancines A1 and B2 as examples of applications of the nitrone intermediate.



CARB 77

Antioxidant activities of two fractions of water-soluble polysaccharide from mung bean (*Vigna Radiata* L.) hull by ultrasonic assisted extraction

Fu-rao Lai[1], furaolai@gmail.com, Hui Wu[2], fehwu@scut.edu.cn, Xiao-feng Li[2], xflibio@scut.edu.cn, Qi-biao Wen[3], lfqbwen@scut.edu.cn, and ***Hui-ning Xiao***[4]*, hxiao@unb.ca. (1) College of Light Industry and Food Sciences, South China University of Technology, 381# Wushan Road, Tianhe District, Guangzhou 510640, China, Fax: +86-20-87112853, (2) College of light industry and food sciences, South China University of Technology, 381# Wushan Road, Tianhe District, Guangzhou 510640, China, (3) College of Light Industry and Food Sciences, South China university of technology, 381# Wushan Road, Tianhe District, Guangzhou 510640, China, (4) Key State Lab of Pulp & Paper Eng, South China University of Technology, 381# Wushan Road, Tianhe District, Guangzhou 510640, China*

Ultrasonic-assisted extraction and antioxidant activity of water-soluble polysaccharide (MSP) from mung bean (*Vigna Radiata* L.) hull were investigated. After deproteinization by Sevag reagent, MSP was isolated and purified by a DEAE-Cellulose anion-exchange column and a Sephadex G-100 gel-permeation column. The achieved two acid polysaccharide fractions, MP1 and MP2, were characterized by FT-IR, GC, and gel permeation chromatography. Results indicated that the molecule weight of MP1 and MP2 were 83kDa and 45kDa, respectively, and their uronic acid contents were 9.93% and 25.37%, respectively. The ratio of monosaccharide components (Rha, Fuc, Ara, Xyl, Man, Gal and Glu) in the two fractions were 0.3:0.13:3.84:1:31.15:9.31:1.06 and 6.86:0.76:3.60:1:2.51:6.28:0.54, respectively. Furthermore, MP1 and MP2 exhibited high superoxide radical-scavenging, hydroxyl radical-scavenging and moderate DPPH scavenging activities at 100μg/mL concentrations. And MP1 showed higher inhibition effect on self-oxidation of 1,2,3-phentriol than MP2. It should be explored as a novel potential antioxidant.

CARB 78

Carbohydrate uptake and utilization of *Clostridium tyrobutyricum* ZJU 8235

Ling Jiang, elicjiang@zju.edu.cn, School of Bioscience and Bioengineering, South China University of Technology, Wu shan Road 381, Guangzhou 510640, China, Fax: +86-20-39380626, ***Jufang Wang****, jufwang@scut.edu.cn, School of Bioscience and BioengineeringSouth, China University of Technology, Wu shan Road 381, Guangzhou 510640, China, Fax: +86-20-39380626, Shizhong Liang, School of Bioscience and Bioengineering, South China University of Technology, Guangzhou 510640, China, Peilin Cen, Dept. of Chemical and Biochemical Engineering, Zhejiang University, Hangzhou 310027, China, and Zhi Nan Xu, znxu@zju.edu.cn, Department of Chemical and Biochemical Engineering, Zhejiang University, Hangzhou 310027, China*

The saccharolytic clostridia are a diverse group of obligate anaerobic bacteria with potential for the fermentative production of chemicals and solvents. Several species exhibit a broad substrate range, but there have been few studies of the mechanisms involved in regulation of uptake and metabolism of fermentable carbohydrates. The utilization of three monosaccharides and three disaccharides by Clostridium tyrobutyricum ZJU 8235 was investigated. Phosphorylation of glucose, fructose, xylose, sucrose, maltose and cellobiose by toluene-treated cells was supported by phosphoenolpyruvate, indicating the involvement of a phosphotransferase system in uptake of these substrates. Furthermore, extract fractionations and PTS reconstitution experiments revealed that both soluble and membrane components are required for the phosphotransferase activities. The presence of phosphotransferase activities in extracts prepared from cells grown on different carbon sources correlated with transport activities in whole cells, and the pattern of transport activities reflected the substrate preference of cells growing in the presence of glucose and another carbon source. Understanding these processes is therefore critical in establishing a productive fermentation, the objective of which is to generate the maximum conversion of a cheap growth substrate into a commercially valuable product.

CARB 79

Synthesis and biological evaluation of glycoporphyrins

Joao P. C. Tome*, jtome@ua.pt, Leandro M. O. Lourenço, Maria G. P. M. S. Neves, and Jose A. S. Cavaleiro, Department of Chemistry, University of Aveiro, Campus Santiago, Aveiro, 3810-193, Portugal, Fax: 00351234370084*

Porphyrin and sugar derivatives constitute two groups of natural compounds which play key roles in many vital functions to our life. The attachment of

saccharide units to porphyrin macrocycles gives rise to derivatives which might be of great significance for certain medicinal and other applications. Glycoporphyrin derivatives and related compounds have been synthesised and evaluated as photosensitizers (PS) on photodynamic therapy (PDT) of oncological, cardiovascular, dermatological, ophthalmic and infectious diseases.

PDT is based on the PS concentration in target cells and, upon subsequent irradiation with visible light in the presence of oxygen, with specific destruction of the target cells/tissues. For an ideal PS, both the photophysical and the hydrophobic/hydrophilic properties of a PS are important parameters to have in consideration.

As part of our program on the development of glycoporphyrin derivatives with potential use in medicine, we will discuss the synthesis of new porphyrin-D-galactose conjugates, their structural characterization, photophysical and antiviral results against HSV-1 (based on the presence of the D-galactose moiety with protected or unprotected hydroxyl groups and the influence of their neutral or cationic features).

Thanks are due to QOPNA and to FCT (Fundação para a Ciência e a Tecnologia, Lisbon) and FEDER (project PTDC/QUI/65228/2006) for funding this work.

CARB 80

Analysis of heparin microarrays using MALDI-TOF-TOF allows for high-throughput analysis of heparin degradation

Hope E. Stansfield*, stansh@rpi.edu, Departments of Chemistry and Chemical Biology, Rensselaer Polytechnic Institute, Biotech Center 4005, 110 8th Street, Troy, NY 12180, Tatiana N. Laremore, Department of Chemistry and Chemical Biology, Rensselaer Polytechnic Institute, Troy, NY 12180, Wenjing Zhao, zhaow4@rpi.edu, Department of Biology, Rensselaer Polytechnic Institute, 110 8th Street, Troy, NY 12180, Jonathan S. Dordick, Department of Chemical and Biological Engineering and Rensselaer Nanotechnology Center, Rensselaer Polytechnic Institute, 110 8th Street, Troy, NY 12180, and Robert J. Linhardt, linhar@rpi.edu, Department of Chemistry and Chemical Biology, Department of Chemical and Biological Engineering, Department of Biology, Rensselaer Polytechnic Institute, Troy, NY 12180*

High-throughput analysis of enzymatic heparin degradation may be effected by the printing of *w*-hydrazido adipyl-azo-linked heparin in microarray format on TiO_2-coated borosilicate slides. Recombinant heparin lyase enzymes may be used, before or after printing, to digest the heparin into its constitutive disaccharides. These disaccharides may be detected by exploiting the

conductive properties of TiO_2-coated borosilicate by the use of MALDI-TOF-TOF, an analysis method well suited for the detection of disaccharides.

CARB 81

Biochemically engineered heparin

***Zhenyu Wang**, wangz2@rpi.edu, Department of Biology, Rensselaer Polytechnic Institute, 110 8th St., Troy, NY 12180, Zhenqing Zhang, zhangz5@rpi.edu, Department of Chemistry, RPI, 110 8 th st, troy, NY 12180, Wenjing Zhao, zhaow4@rpi.edu, Department of Biology, Rensselaer Polytechnic Institute, 110 8th Street, Troy, NY 12180, Fuming Zhang, zhangf2@rpi.edu, Department of Chemical and Biological Engineering, Rensselaer Polytechnic Institute, Center for Biotechnology and Interdisciplinary Studies, 110 8th Street, Troy, NY 12180, and Robert J. Linhardt, linhar@rpi.edu, Department of Chemistry and Chemical Biology, Department of Chemical and Biological Engineering, Department of Biology, Rensselaer Polytechnic Institute, Troy, NY 12180*

Heparin is a very wildly used anticoagulant drug. However, the current USP heparin production from porcine intestine has many drawbacks and poses potential issue for the quality control and raw material supply of heparin. To overcome these drawbacks, our lab proposed a new method to produce heparin, which starts from the fermentation production of heparosan, and then goes through a few chemoenzymatic modification steps to produce anticoagulant heparin. The heparosan fermentation was further engineered to increase the heparosan yield, and the heparosan chemoenzymatic modification steps were controlled to produce product that resemble the animal-source heparin.

CARB 82

Chemoenzymatic synthesis of a new class of macrocyclic oligosaccharides

***Saddam Muthana**, smmuthana@ucdavis.edu and Xi Chen, chen@chem.ucdavis.edu, Department of Chemistry, University of California, Davis, One Shields Avenue, Davis, CA 95616*

Macrocyclic carbohydrates have found widespread and diverse applications such as building blocks in supramolecular chemistry, drug carrier systems, and artificial receptors. We have developed a novel and highly efficient chemoenzymatic method for the preparation of structurally-defined macrocyclic oligosaccharides of varied sizes. This method involves chemical or chemoenzymatic synthesis of oligosaccharides containing a galactose at the non-reducing end and a propargyl group at the reducing end as sialyltransferase

acceptors. Introducing an azido-containing sialic acid to the non-reducing end of the galactosides through a sialyltransferase-catalyzed enzymatic reaction followed by copper(I)-catalyzed Huisgen's 1,3-dipolar cycloaddition of alkyne and azide provides size-defined macrocyclic carbohydrates. The produced negatively charged macrocycles have high solubility in water and interact with hydrophobic small molecules.

CARB 83

Conformational studies of lacto-*N*-fucopentaose 2 using NMR spectroscopy and molecular simulations

Elin Säwén[1]*, elin@organ.su.se, Florian Hinterholzinger*[2]*, Clas Landersjö*[1]*, and Göran Widmalm*[1]*, gw@organ.su.se. (1) Department of Organic Chemistry, Stockholm University, Arrhenius Laboratory, Stockholm S-10691, Sweden, Fax: +46 8 15 49 08, (2) Department of Organic Chemistry, Stockholm University, Arrhenius laboratory, Stockholm S-10691, Sweden*

Milk oligosaccharides are the third largest constituent of human breast milk. The composition of the milk oligosaccharides differ for milk from different mothers and are dependent on the Lewis blood group of the mother. These oligosaccharides have been found to be important for the immune system of infants. Milk oligosaccharides can for example prevent the binding of toxins to cellular targets. Knowledge of the solution structure of milk oligosaccharides is important for the understanding of molecular recognition processes.

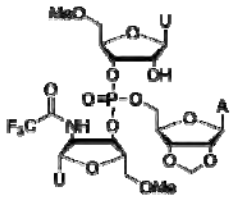
We have studied the conformation of the human breast milk oligosaccharide Lacto-*N*-fucopentaose 2 (LNF-2). Studies were carried out by NMR spectroscopy in solution. Heteronuclear long-range coupling constants over the glycosidic linkages were measured with the J-HMBC experiment. Effective $^{1}H,^{1}H$ distances were derived from $^{1}H,^{1}H$ 2D-NOESY measurements. The solution structures from NMR spectroscopy were compared to results from molecular dynamics and Langevin dynamics simulations.

CARB 84

Elucidating the role of a hydrogen bond donor at the 2'-position of the 3'-linked departing nucleoside in transesterification by large ribozymes: Hydrolytic reactions of 2',3'-O-methyleneadenosin-5'-yl 5'-O-methyluridin-3'-yl 5'-O-methyl-2'-trifluoroacetamido-2'-deoxyuridin-3'-yl phosphate

Tuomas A. Lönnberg*, tuanlo@utu.fi and Maarit Laine, Department of Chemistry, University of Turku, Vatselankatu 2, Turku FIN-20014, Finland, Fax: +358-2-333-6700*

2',3'-O-Methyleneadenosin-5'-yl 5'-O-methyluridin-3'-yl 5'-O-methyl-2'-trifluoroacetamido-2'-deoxyuridin-3'-yl phosphate (1), a trinucleoside-3',3',5'-monophosphate having one of the 2'-OH groups of the 3'-linked nucleosides replaced by a stronger hydrogen bond donor (the trifluoroacetamido group), has been prepared and its hydrolytic reactions followed by RP HPLC over a wide pH range. At pH < 2, disappearance of 1 is first-order in [H+] and 9 times as rapid as that of the 2'-OH counterpart 2, with cleavage of the P-O3' being slightly favored. At pH > 4, the reaction is first-order in [HO-] and 1 is hydrolyzed 2.3 times as rapidly as 2, with P-O3' bond cleavage predominating. Between pH 2 and 4, the reaction is pH-independent and cleavage of the P-O3' and P-O5' bonds proceed at comparable rates. The effect of the superior hydrogen bond donor at the 2'-position of the 3'-linked departing nucleoside on the rate of hydrolysis of the P-O3' and P-O5' bonds and implications for the cleavage mechanism of large ribozymes are discussed.



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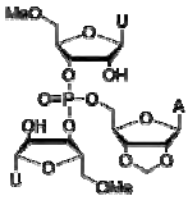


2

CARB 85

Solution structures of chemoenzymatically synthesized heparin and its precursors

Zhenqing Zhang[1]*, zhangz5@rpi.edu, Scott A. McCallum*[2]*, Jin Xie*[3]*, Xiej@rpi.edu, Lidia Nieto*[4]*, Francisco Corzana*[4]*, Jesu´s Jime´nez-Barbero*[4]*, Jian Liu*[5]*, liuj@email.unc.edu, and Robert J Linhardt*[6]*, linhar@rpi.edu. (1) Department of Chemistry, RPI, 110 8 th st, troy, NY 12180, (2) Director, NMR Core Facility, Center for Biotechnology and Interdisciplinary Studies, Rensselaer Polytechnic Institute, 110 8th Street, Troy, NY 12180, (3) Rensselaer Polytechnic Institute, troy 12180, (4) Span, (5) Division of Medicinal Chemistry and Natural Products, University of North Carolina, Chapel Hil, NC 27599, (6) Departments of Chemistry and Chemical Biology, Rensselaer Polytechnic Institute, Center for Biotechnology and Interdisciplinary Studies, 110 8th Street, Troy, NY 12180*

We report the first chemoenzymatic synthesis of the stable isotope-enriched heparin from a uniformly labeled [13C,15N]N-acetylheparosan (-GlcA(1,4)GlcNAc-) prepared from E. coli K5. Glycosaminoglycan (GAG) precursors and heparin were formed from N-acetylheparosan by the following steps: chemical N-deacetylation and N-sulfonation leading to N-sulfoheparosan (-GlcA(1,4)GlcNS-); enzymecatalyzed C5-epimerization and 2-O-sulfonation leading to undersulfated heparin (-IdoA2S(1,4)GlcNS-); enzymatic 6-O-

sulfonation leading to the heparin backbone (-IdoA2S(1,4)GlcNS6S-); and selective enzymatic 3-O-sulfonation leading to the anticoagulant heparin, containing the GlcNS6S3S residue. Heteronuclear, multidimensional nuclear magnetic resonance spectroscopy was employed to analyze the chemical composition and solution structure of [13C,15N]N- cetylheparosan, precursors, and heparin. Isotopic enrichment was found to provide well-resolved 13C spectra with the high sensitivity required for conformational studies of these biomolecules. Stable isotope-labeled heparin was indistinguishable from heparin derived from animal tissues and is a novel reagent for studying the interaction of heparin with proteins.

CARB 86

Analysis of pharmaceutical heparins and potential contaminants using 1H-NMR and PAGE

Zhenqing Zhang[1]*, zhangz5@rpi.edu, Boyangzi Li*[1]*, Jiraporn Suwan*[2]*, suwanj@rpi.edu, Fuming Zhang*[3]*, zhangf2@rpi.edu, Zhenyu Wang*[4]*, wangz2@rpi.edu, Haiying Liu*[5]*, liuh6@rpi.edu, Barbara Mulloy*[6]*, and Robert J Linhardt*[7]*, linhar@rpi.edu. (1) Department of Chemistry, RPI, 110 8 th st, troy, NY 12180, (2) Thailand Excellence Center for Tissue Engineering, Department of Biochemistry, Chiang Mai University, Chiang Mai 50200, Thailand, (3) Department of Chemical and Biological Engineering, Rensselaer Polytechnic Institute, Center for Biotechnology and Interdisciplinary Studies, 110 8th Street, Troy, NY 12180, (4) Department of Biology, Rensselaer Polytechnic Institute, 110 8th St., Troy, NY 12180, (5) Department of Chemistry, Rensselaer Polytechnic Institute, Troy, NY 12180, (6) National Institute for Biological Standards and Control, (7) Departments of Chemistry and Chemical Biology, Rensselaer Polytechnic Institute, Center for Biotechnology and Interdisciplinary Studies, 110 8th Street, Troy, NY 12180*

In 2008, heparin (active pharmaceutical ingredient, API) lots were associated with anaphylactoid-type reactions. Oversulfated chondroitin sulfate (OSCS), a semi-synthetic glycosaminoglycan (GAG), was indentified as a contaminant and dermatan sulfate (DS), a GAG was identified as an impurity. While DS has no known toxicity, OSCS was toxic leading to patient deaths. Heparins, prepared before these adverse reactions needed to be screened for impurities and contaminants. Heparins in different years were analyzed using high-field 1H-NMR spectroscopy. Twenty heparinoids were mixed with heparin and analyzed by 1H-NMR to assess the utility of 1H-NMR for screening heparin adulterants. Sensitivity of heparinoids to deaminative cleavage, a method widely used to depolymerize heparin, was evaluated with polyacrylamide gel electrophoresis to estimate the level of impurities and contamination giving limits of detection (LOD) ranging from 0.1% to 5%. Most pharmaceutical heparins prepared between 1941 and 2008 showed no impurities or contaminants. Some contained DS, CS,

heparan sulfate and sodium acetate impurities. Heparin prepared in 2008 contained OSCS contaminant. Heparin adulterated with heparinoids showed additional peaks in their high-field 1H-NMR spectra, clearly supporting this method for monitoring of heparin API with an LOD of 0.5 to 10%. Most of these heparinoids were stable to nitrous acid treatment suggesting its utility for evaluating impurities and contaminants in heparin API.

CARB 87

Chondroitin lyase action pattern study using LC-MS

Zhenqing Zhang[1]*, zhangz5@rpi.edu, Youmie Park*[2]*, youmiep@yahoo.com, Melissa Kemp*[3]*, kempm@rpi.edu, Wenjing Zhao*[3]*, Miroslaw Cygler*[4]*, Yeong Shik Kim*[5]*, and Robert J Linhardt*[6]*, linhar@rpi.edu. (1) Department of Chemistry, RPI, 110 8 th st, troy, NY 12180, (2) Department of Chemisty and Chemical Biology, Rensselaer Polytechnic Institute, Biotech 4005, 110 8th St, Troy, NY 12180, (3) Department of Biology, Rensselaer Polytechnic Institute, 110, 8th Street, Troy, NY 12180, (4) McGill University, Montreal, Canada, (5) College of Pharmacy, Seoul National University, Seoul, (6) Departments of Chemistry and Chemical Biology, Rensselaer Polytechnic Institute, Center for Biotechnology and Interdisciplinary Studies, 110 8th Street, Troy, NY 12180*

Liquid chromatography-mass spectrometry was applied to determine the action pattern of different chondroitin lyases. Two commercial enzymes (chondroitinase ABC, Proteus vulgaris and chondroitinase ACII, Arthrobacter aurescens) having action patterns previously determined by viscosimetry and gel electrophoresis were first examined. Next, the action patterns of recombinant lyases, chondroitinase ABC from Bacteroides thetaiotaomicron (expressed in Escherichia coli) and chondroitinase AC from Flavobacterium heparinum (expressed in its original host) were examined. Chondroitin sulfate A (CS-A, also known as chondroitin-4-sulfate) was used as the substrate for these four lyases. Aliquots taken at various time points were analyzed. The products of chondroitinase ABC (P. vulgaris) and chondroitinase AC (F. heparimum) contained unsaturated oligosaccharides of sizes ranging from disaccharide to decasaccharide, demonstrating that both are endolytic enzymes. The products afforded by chondroitinase ABC (B. thetaiotaomicron) and chondroitinase ACII (A. aurescens) contained primarily unsaturated disaccharide. These two exolytic enzymes showed different minor products suggesting some subtle specificity differences between the actions of these two exolytic lyases on chondroitin sulfate A.

CARB 88

Distribution of lignin and cellulose in cell walls of *Cornus alba*

***Feng Xu**, xfx315@bjfu.edu.cn, College of Materials Science and Technology, Beijing Forestry University, Beijing, China, Qinghua North Road 35, Beijing 100083, China, Fax: +86-10-62338460, Jianzhen Mao, College of Chemistry and Chemical Engineering, Qiqihar University, 42 Wenhua Street, Qiqihar 161006, China, Xinchun Zhong, College of Light and Textile Industry, Qiqihar University, Wenhua Street, Qiqihar 161006, China, and Hong Zhao, redbud99@sohu.com, College of Light and Textile Industry, Qiqihar University, Wenhua Street 42, Qiqihar 161006, China*

Many species of shrubs are applied in a wide range of economic uses and therefore the chemical and mechanical properties are of great importance. Cornus alba is one of these shrub. The lignin and cellulose distribution within the cell walls of Cornus alba were studied topochemically by means of Raman microscope. Chemical information in different anatomical regions was obtained according to Raman images of lignin and cellulose spatial distribution. The maximum lignin concentration was shown to be located in cell corner (CC), whereas the cellulose concentration revealed a minimum. While lignin concentration in compound middle lamella (CML) was higher than that in S2, distribution of cellulose showed the opposite pattern. The CC-to-S2 lignin concentration ratio was suggested not to be higher than 4.

Keywords: lignin; cellulose; Cornus alba, Raman microscope

CARB 89

Lessons learned from the contamination of heparin

*Haiying Liu[1], liuh6@rpi.edu, **Zhenqing Zhang**[1], zhangz5@RPI.EDU, and Robert J. Linhardt[2], linhar@rpi.edu. (1) Department of Chemistry, Rensselaer Polytechnic Institute, Troy, NY 12180, (2) Department of Chemistry and Chemical Biology, Department of Chemical and Biological Engineering, Department of Biology, Rensselaer Polytechnic Institute, Troy, NY 12180*

Heparin is a polydisperse mixture of linear acidic polysaccharides having anticoagulant and antithrombotic activities. Heparin is unique as one of the oldest drugs currently still in widespread clinical use, a natural product, one of the first biopolymeric drugs, and one of the few carbohydrate drugs. Pharmaceutical heparin is prepared in ton quantities from the mast cell-rich tissues, lung and intestine. Recently, certain batches of heparin have been associated with anaphylactoid-type reactions, some leading to hypotension and death. These reactions were traced to a contamination with a semi-synthetic oversulfated chondroitin sulfate (OSCS). OSCS is prepared by chemical sulfonation of the structurally related chondroitin sulfate. OSCS exerts a profound effect on Factor XIIa resulting in enhanced bradykinin production leading to hypotension. Dermatan sulfate, a natural polysaccharide impurity with no known toxicity was

also present in contaminated heparin. OSCS also carried over into low molecular weight heparins. The suspicious origin of the semi-synthetic OSCS has led pharmaceutical scientists to examine dozens of natural and synthetic heparinoids as potential heparin contaminants. Effective assays, which can detect both known and unknown contaminants, are being developed to monitor the quality of heparin. Safer and better-regulated processes are needed for heparin production. A chemo-enzymatically synthesized heparin has recently been successful prepared in milligram quantities. Kilogram quantities of such a bioengineered heparin would support human clinical trails and ton-scale production would be needed to replace animal sourced heparin.

CARB 90

Regioselective glycosylation of mannose diols: Studies toward a more efficient synthesis of high mannose type oligosaccharides

Jane M. Kalikanda*, jkalika1@binghamton.edu and Zhitao Li, Department of Chemistry, Binghamton University, Binghamton, NY 13902*

As part of our effort to develop an efficient synthesis of high mannose oligosaccharides,the reactivity of 2,3-mannose diol acceptors was studied and predicted using computational methods. Glycosylation of several such acceptors was conducted using selected donors. Highly regioselective results were obtained and regioselectivity was found to be both donor and acceptor dependent.

CARB 91

Computational analysis of carbohydrates processing for *Enterococcus faecalis* and *Escherichia coli*

James Shelton[1]*, james.shelton@smail.astate.edu, Brittany L. Bailey*[2]*, brittany.bailey@smail.astate.edu, Kayla Watkins*[1]*, kayla.watkins@smail.astate.edu, Christopher Saito*[3]*, christopher.saito@smail.astate.edu, Jessica Lack*[1]*, jessica.lack@smail.astate.edu, Ebony Love*[1]*, ebony.love@smail.astate.edu, Tony James*[1]*, tony.james@smail.astate.edu, Earl Benjamin III*[1]*, earlbenjamin@astate.edu, and Ellis Benjamin*[1]*. (1) The Applied Molecular & Synthetic Lab: Department of Chemistry and Physics, Arkansas State University, PO Box 419, State Univerisity, AR 72467, (2) The Applied Molecular & Synthetic Lab: Department of Biology, Arkansas State University, PO Box 419, State Univerisity, AR 72467, (3) The Applied Molecular & Synthetic Lab: Department of Chemistry and Physics, Arkansas State University, PO Box 419, State University, AR 72467*

Present in most food products, high fructose corn syrup is currently being used to sweeten everything from soft drinks to candy. Previous studies have shown that the presence of various sugars may play and integral role in bacterial growth and food spoilage. Although studies have determined the metabolic processing of high fructose corn syrup in bacteria such as *Enterococcus faecalis* and *Escherichia coli*, few studies have analyzed this mechanism using computational methods. Computational analyses for the catalytic breakdown of fructose, glucose, sucrose, sorbitol were conducted utilizing binding energies of catabolic enzymes found in *Escherichia coli* and *Enterococcus faecalis* to overall binding energies as well as force and shape binding energies. The results suggest that even minor variations in structural caused changes binding. Results even showed differences in the binding energy between the linear and the ring forms of the sugar suggesting that the sugar form may also play a role in sugar metabolism. This investigation has far reaching implications for food spoilage.

CARB 92

Structural specificity of gp120 carbohydrates for binding to HIV-fusion blocking cyanobacterial proteins determined by NMR and other biophysical techniques

***Syed Shahzad ul Hussan**, hussans@mail.nih.gov, Ali B. Shah, and Carole A. Bewley, Laboratory of Bioorganic Chemistry, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, 9000 Rockville Pike, Bethesda, MD 20892*

Number of cyanobacterial lectins has been identified in recent years as the potential antiviral candidates on account of their binding ability to envelope carbohydrates of virus. We have described here the structural specificities of gp120 carbohydrates required for binding to two cyanobacterial lectins. These lectins by binding to gp120 inhibit the fusion of HIV-1 to the host cell. We have also described the enzymatic ability of one these two lectins which cleaves the straight chain chitooligosaccharides into monosaccharides. Saturation Transfer Difference (STD), chemical shift mapping and intermolecular NOE techniques of NMR, Isothermal Titration Calorimetry (ITC) and site-directed mutagenesis methodologies were used in these studies. Microcystis aeruginosa lectin MVN shares 33 % identity with known potent anti-HIV protein cyanovirin-N. We have studied the binding specificity of this lectin using fragment-based approach of high-mannose carbohydrates and determined the solution structure partly by using three-dimensional NMR experiments. Microcystis viridis lectin (MVL) is known to recognize Man2A, a tetrasaccharide as the smallest structure of the high-mannose carbohydrates of gp120. Our results suggested GlcNAc2, a disaccharide, as the smallest carbohydrate unit recognized by this protein. MVL was also found having enzymatic ability to cleave glycosidic linkage of GlcNAc2 and straight chain chitooligosaccharides into N-acetyl glucosamine. Analysis

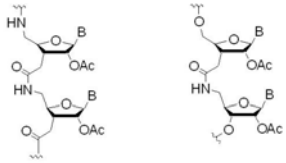
based upon site directed mutagenesis revealed only one of the two carbohydrate binding sites of this protein was involved in the enzymatic activity and aspartic acid-75 and glutamic acid-76 were identified as the key residues involved in the catalytic hydrolysis. These two lectins with different structural properties and different binding specificities, therefore, represent important leads for the anti-HIV protein.

CARB 93

Synthesis and properties of amide modified RNA analogs

Paul Tanui[1], *ptanui1@binghamton.edu, Chelliah Selvam*[2], *Siji Thomas*[3], *Jason Abbott*[3], *Martin Kullberg*[3], *and Eriks Rozners*[1], *erozners@binghamton.edu. (1) Department of Chemistry, Binghamton University, PO BOX 6000, Binghamton, NY 13902, Fax: 607 777 4478, (2) Department of Chemistry, Binghamton University, PO BOX 6000, Binghamton, NY 13905, (3) Department of Chemistry and Chemical Biology, Northeastern University, Boston, MA 02115*

The recent discovery of RNA interference has provided a potent and specific method for controlling gene expression in human cells, which strongly impacted broad areas of modern biology ranging from functional genomics to drug discovery. For potential in vivo applications, small interfering RNAs (siRNA) require chemical modification to fine-tune the thermal stability, increase the cellular delivery, potency and in vivo half-life of the RNA dublexes. Amides as nonionic non-phosphorus internucleoside linkages are remarkably good mimics of the phosphodiester linkage in RNA and potential modifications for siRNAs. However, the progress in the field has been hampered by shortage of efficient methods to synthesize the monomeric building blocks to prepare amide modified RNA analogues. This presentation will highlight new synthetic strategies for synthesis of monomeric building blocks required for the synthesis of amide modified RNA. Synthesis and biophysical properties of amide modified RNA fragments will be also discussed.



CARB 94

Glycosylation characterization of recombinant intrinsic factor

Lianli Chi[1]*, lianli.chi@abbott.com, Carol S. Ramsay*[1]*, Carol.Ramsay@abbott.com, Jeffrey R. Fishpaugh*[2]*, jeffrey.fishpaugh@abbott.com, You Pan*[3]*, you.pan@abbott.com, and Gerard J. Davis*[3]*. (1) Abbott Diagnostics Division, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064, Fax: 847-938-7550, (2) Abbott Diagnostics Division, Abbott Laboratories, 100 Abbott Park Road, Abbott Park, IL 60064-3502, (3) Abbott Diagnostics Division, Abbott Laboratories, 100 Abbott Park Rd, Abbott Park, IL IL60064-3500*

Mammalian cell produced recombinant proteins are widely used in the pharmaceuticals and diagnostics industries. Characterization of mammalian cell produced recombinant proteins sometimes is difficult due to complicated glycosylation. The glycosylation may be an important factor for recombinant proteins functioning similarly as analogs of the native proteins. Therefore it is important to characterize the glycosylation pattern of recombinant glycoproteins. In this study, a mammalian cell produced recombinant intrinsic factor (rIF) was analyzed using mass spectrometry. The degree of glycosylation was demonstrated using MALDI-TOF-MS. The glycosylation sites were determined using LC/MS/MS. The glycans were released using enzymatic or chemical methods and their structures were elucidated using LC/MS. By using various mass spectrometric methods, the complex glycosylation of rIF was successfully characterized.

CARB 95

Purification of carbohydrates by medium pressure liquid chromatography

Jack E. Silver*, jsilver@teledyne.com, Ellen Bilger, Timothy R. Crea, and Ruth Pipes, Teledyne Isco, 4700 Superior Street, Lincoln, NE 68504, Fax: 402-465-3091*

The purification of carbohydrate compounds and intermediates has proven difficult because of low adsorbing and absent chromophores. Advances in MPLC equipment and media allow faster and improved purification, saving time and solvent. Examples of detection and purifications will be shown.

CARB 96

Boronic acid-modified TTP analogs for the selection of DNA-based aptamers for glycoproteins

Yunfeng Cheng[1]*, jerry_cyf@hotmail.com, Shan Jin*[2]*, Shilong Zheng*[1]*, Chaofeng Dai*[1]*, Minyong Li*[1]*, and Binghe Wang*[1]*, wang@gsu.edu. (1) Department of Chemistry and Center for Biotechnology and Drug Design, Georgia State University, 50 Decatur Street, Atlanta, GA 30303, (2) Department of Chemistry and Center for Biotechnology and Drug Design, Georgia State University, 50 Decatur Street, atlanta, GA 30303*

Glycosylation plays critical roles in determining the functions and fates of proteins. The ability to analyze and differentiate variations of glycosylation patterns in a given glycoprotein is of tremendous value for the development of new diagnostics and biomedical research tools. We have reported that incorporation of the boronic acid moiety into DNA allows aptamer selection to gravitate toward the glycosylation site and therefore for the specific recognition of the glycosylation site. Herein we report our successful rational design and synthesis of four additional boronic acid-modified TTP analogs for incorporation into DNA based on molecular simulation results. These analogs were more readily obtained with shorter synthetic routes and higher total yields compared with the boronic acid-modified TTP reported earlier. All four analogs were recognized as a substrate by DNA polymerase, and then effectively incorporated into DNA in both primer extension and PCR. The availability of these boronic acid-modified TTPs will increase the structural diversity needed for DNA aptamer selection for a large set of glycoproteins and carbohydrates.

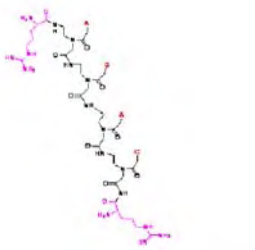
CARB 97

Peptide nucleic acid analogs for sequence selective RNA recognition

Oluwatoyosi Muse*, tmuse1@binghamton.edu, Department of Chemistry, Binghamton University, Binghamton, NY 13902, Fax: 6077774478, Ming Li, Department of chemistry, Binghamton University, NY 13902, and Eriks Rozners, erozners@binghamton.edu, Department of Chemistry, Binghamton University, PO BOX 6000, Binghamton, NY 13902*

RNA is an attractive drug target because of the central role it plays in gene expression. Most of the current drugs bind their RNA target strongly in a shape selective manner but with low selectivity, which may cause severe side effects in clinic. A hydrogen bond mediated sequence selective binding of RNA, such as triple helix formation, has the potential of high selectivity but is typically weak and underutilized in current drug design. We propose that chemically modified Peptide Nucleic Acids (PNA) may bind both strongly and sequence selectively to double stranded RNA of therapeutic relevance, including HIV-1 TAR RNA. Such binding would have potential for development of novel antibiotics and antiviral drugs. This presentation will discuss design, synthesis and binding studies of modified PNA. Our preliminary results obtained using UV and Fluorescence

spectroscopy and Isothermal Titration Calorimetry show that PNA binds very strongly to double stranded RNA targets - Ka~3X108 M-1.

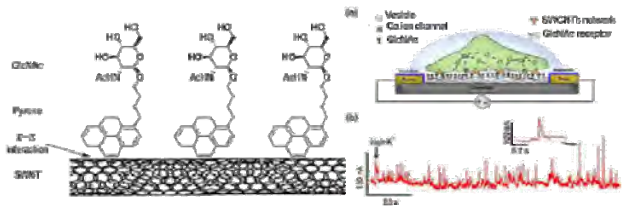


CARB 98

Carbohydrate coating of carbon nanotubes for detection of cell secretion

Jimei Ma[1]*, maji0004@ntu.edu.sg, Simon Ng*[1]*, Herry Gunadi Sudibya*[2]*, Peng Chen*[2]*, and Xue-Wei Liu*[1]*, xuewei@ntu.edu.sg. (1) Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, 21 Nayang Link, Singapore 637371, Singapore, (2) Division of Bioengineering, School of Chemical and Biomedical Engineering, Nayang Technological University, 70 Nanyang Avenue, Singapore 637457, Singapore*

Carbohydrate-carbohydrate or carbohydrate-lectin interactions play a vital role in biological process such as cell-cell recognition, immunological response, metastasis, and fertilization. These interactions and consequent cellular events can be studied by interfacing carbohydrate-coated carbon nanotube network devices with living cell. In this work, we firstly fabricated thin-film networks of single-walled carbon nanotubes (SWCNTs) by interacting with glycoside-coupled pyrene. This network device interfaced biocompatibly with living cells, improving PC12 cell adhesion and growth. As a biosensor, the device aided to electrochemically detect the dynamic secretion of biomocecules. This unique approach provides real-time and noninvasive measurements from living cells with high sensitivity, high temporal resolution, high throughput and ease of detection. This study is another example of seamless combination of nanotechnology and glycobiology.



CARB 99

Development of an indium-mediated tandem carbon-carbon bond forming reaction: Application to the synthesis of C-aryl glycosides

Thomas G. Minehan, *thomas.minehan@csun.edu, John Alec Moral, Seong-Jin Moon, and Samuel Rodriguez-Torres, Department of Chemistry and Biochemistry, California State University, Northridge, 18111 Nordhoff Street, Northridge, CA 91330, Fax: (818) 677-4068*

Indium-mediated allylation of aldehydes with 2,3-dichloropropene, followed by a palladium-catalyzed cross-coupling reaction with arylindium reagents, leads to aryl-substituted homoallylic alcohols in good yields and diastereoselectivities. The products obtained from coupling reactions with D-glyceraldehyde acetonide can be transformed into 2-deoxy-ß-C-aryl ribofuranosides in high overall yields. Similarly, 2-deoxy-ß-C-aryl glucopyranosides may be prepared in an efficient 4-step route from a benzylidene-protected aldotetrose.

CARB 100

One-pot rhodium-catalyzed aziridination and ring-opening of glycal: A direct access to 2-amino sugars and its application to synthesis of sialic acids

Xuewei Liu, xuewei@ntu.edu.sg and ***Rujee Lorpitthaya****, g050010@ntu.edu.sg, Division of Chemical and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, 21 Nanyang Link, Singapore 637371, Singapore, Fax: 656-791-1961*

The flexible installation of a sulfamate moiety on different positions of the glycal scaffold has been highlighted to be a new concept for synthesizing a- and b-aminoglycosides (Figure 1). The methodology incorporates to three relevant steps: 1) the introduction of the sulfamate-ester on C3, C4, and C6 of glycal, 2) the intramolecular rhodium-catalyzed aziridination, and 3) regio- and stereoselective ring-opening of aziridines. With this rational design of substrates, the possibility, reactivity and limitation of forming aziridine-ring intermediates from **1**, **2**, and **3** will be performed based on the results from experimental observations and DFT calculations.

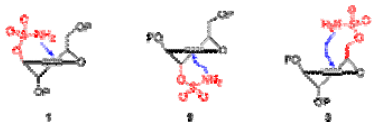


Figure 1

We furthermore have developed our methodology for the selective *C*-glycosylation via one-pot rhodium-catalyzed aziridination and indium-mediated allylation at the anomeric position (Figure 2). The reaction underwent in regio- and stereoselective manners to give 8-membered oxathiazepanes in good to excellent yields. This synthesis is an alternative route to naturally occurring sialic acids and derivatives.

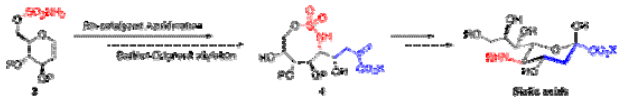


Figure 2

CARB 101

Computationally and experimentally derived general rules for fragmentation of various glycosyl bonds in sodium adduct oligosaccharides

Hiroaki Suzuki, Computational Biology Research Center (CBRC), National Institute of Advanced Industrial Science and Technology (AIST), 2-41-6 Aomi, Koto-ku, Tokyo 135-0064, Japan, and ***Kazuhiko Fukui****, k-fukui@aist.go.jp, Computational Biology Research Center (CBRC), National Institute of Advanced Industrial Science and Technology (AIST), 2-42 Aomi, Koto-ku, Tokyo 135-0064, Japan, Fax: 81-3-3599-8491*

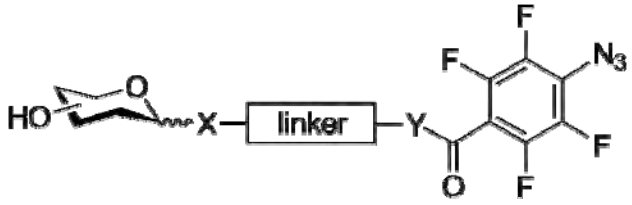
Mechanisms of fragmentation of glycosyl bond linkages in various saccharides were investigated by using computational calculations to find general rules of fragmentation of sodiated oligosaccharides in mass spectrometry. The calculations revealed that α-Glc, α-Gal, β-Man, α-Fuc, β-GlcNAc, and β-GalNAc linkages were cleaved more easily than β-Glc, β-Gal, and α-Man linkages. Comparison of activation energies and binding affinities to the sodium cation revealed an increase in activation energy in proportion to the increment in binding affinity. The order of the calculated activation energies for fragmentation mechanisms was mostly correlated with the stability of the glycosyl bonds in mass spectrometry, indicating that the stabilities of various linkages in mass spectrometry can well be explained by the theoretical calculations. These theoretically and experimentally derived general rules for fragmentation should be useful for analyzing the experimentally obtained mass spectra of N-linked and O-linked oligosaccharides.

CARB 102

Synthesis of novel photoreactive PFPA-carbohydrates for study of carbohydrate-protein interactions

Lingquan Deng[1]*, lingquan@kth.se, Oscar Norberg*[1]*, oscar3@kth.se, Suji Uppalapati*[2]*, suji@pdx.edu, Mingdi Yan*[2]*, yanm@pdx.edu, and Olof Ramstrom*[1]*, ramstrom@kth.se. (1) Department of Chemistry, Royal Institute of Technology, Teknikringen 30, S-100 44 Stockholm, Sweden, (2) Department of Chemistry, Portland State University, 1719 SW 10th Ave., Portland, OR 97201*

Carbohydrate involved recognition events, for example, carbohydrate-protein interactions, play an essential role in many biological processes. To elucidate those recognition events at a molecular level, new methods and techniques are in high demand. The combination of carbohydrate chemistry and surface chemistry provides an efficient solution in this context. In the present study, a number of light-activatable perfluorophenylazide (PFPA)-tagged carbohydrates have been synthesized. The product molecules were all composed of three parts: a carbohydrate moiety, a linker and a PFPA moiety. New synthetic pathways were developed, resulting in good yields in few steps. The influences of the structures on target carbohydrate-protein interactions for a range of lectins have been investigated by several independent techniques, including surface plasmon resonance (SPR), X-ray photoelectron spectroscopy (XPS), etc.



CARB 103

The synthesis of macrocyclic compounds based on glucuronic acid as putative tumor cell migration inhibitors

Dandan Yan*, dandan.yan@ucd.ie, Centre for Synthesis and Chemical Biology, University College Dublin, Belfield, Dublin 4, Dublin, Ireland*

Synthesis of Macrocyclic Compounds Based on Glucuronic Acid as Putative Tumour Cell Migration Inhibitors

Dandan Yan and Paul V. Murphy

School of Chemistry and Chemical Biology, University College Dublin, Belfield, Dublin 4, Ireland.

E-mail: dandan.yan@ucd.ie

Migrastatin 1 and its analogues 3, including isomigrastatin 2 are inhibitors of tumor cell migration. The migration of tumor cells is part of the complex process

of metastasis, which is the leading cause of death in cancer patients.1 Therefore, migrastatin and analogs hold great potential as therapeutic agents for the treatment of cancer. Bewley et al.3 have prepared the new synthetic 12- and 14-membered macrolides such as compound 4 which has structural similarity to 2. These compounds are derived from a pentenoic or heptenoic acid and quinic acid. The most potent compound identified from the quinic acid analogue series is compound 4. This initiated our interest in the synthesis of a series of macrolactones based on glucuronic acid 5 with similar features. The synthesis of 5 and analogues will be outlined.

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CARB 104

Facile synthesis and antitumor cell activity of Se-containing nucleosides

Lina Lin[1]*, linlina2000@yahoo.com, Jia Sheng*[2]*, jsheng1@student.gsu.edu, Razin K Momin*[2]*, rmomin2@student.gsu.edu, Quan Du*[3]*, and Zhen Huang*[4]*, Huang@gsu.edu. (1) Department of Biology and Chemistry, Georgia State University, 50 Decatur street, NSC548, Atlanta, GA 30303, (2) Department of Chemistry, Georgia State University, Atlanta, GA 30303, (3) Department of Chemistry, Brooklyn College, Graduate School and University Center, City University of New York, 2900 Bedford Avenue, Brooklyn, NY 11210, (4) Department of Chemistry, Georgia State Unversity, 38 Peachtree Center AVe, Atlanta, GA 30303*

Many organic compounds containing selenium have shown anticancer effects and some have been used in chemoprevention of cancers and other diseases. Methylselenol (MeSe) was considered to be the most active metabolite of selenium compounds in selenium chemoprevention. It has been well-demonstrated that selenomethionine, containing MeSe functionality, is better absorbed and retained in body than inorganic selenite. In addition, the natural nucleosides may also be used as Se-carriers for these important applications. Several selenonucleobases and 8-seleno-cGMPs were reported with anticancer activities. By taking advantage of our experiences in selenium-derivatized nucleic acids (SeNA), we have designed and synthesized several novel nucleosides derivatized with MeSe functionality at the 2', 3' and 5' positions of the ribose in

order to evaluate the MeSe effect and develop better Se-carriers for anticancer application and chemoprevention. Our work demonstrates for the first time the anticancer activity of the methylseleno nucleosides against prostate cell lines.

CARB 105

Selenium derivatization of human telomeric DNA for structure and function study

Tian Tian[1]*, cindy0069@gmail.com, Jia Sheng*[2]*, jsheng1@student.gsu.edu, Xiang Zhou*[1]*, xzhou@whu.edu.cn, Shaoru Wang*[1]*, and Zhen Huang*[3]*, Huang@gsu.edu. (1) College of Chemistry and Molecular Science, Wuhan University, Luojiashan, Wuchang District, Wuhan 430072, China, (2) Department of Chemistry, Georgia State University, Atlanta, GA 30303, (3) Department of Chemistry, Georgia State Unversity, 38 Peachtree Center AVe, Atlanta, GA 30303*

Human telomeric DNA sequence (TTAGGG repeats) has become an interesting target for antitumor drug design because of its close link to telomerase, which has been found to be overexpressed in 80-90% human tumor cells. It is well known that telomere G-quadruplex has multiple conformations in physiological conditions, which makes it challenging to target. To further explore its structure and function by X-ray crystallography and selenium-derivatized nucleic acids (SeNA), in this work, we have systematically incorporated selenium functionality (2'-SeMe) into several thymidine residues in different loop regions of this telomeric sequence in order to facilitate structural and functional studies. In addition, we have used this strategy to explore the possibility of different stabilized conformations for structure characterization. Through binding with small molecules (such as porphyrin like compounds), the G-quadruplex structures of the modified DNA sequences were studied and compared with the native counterpart by our CD experiments. It has been found that this Se-modification could lead to the different topology of G-quadruplex-small molecule complex, which indicates that in addition to its structural application in X-ray crystallography, this derivatization could also have the potential to serve as an atomic probe in DNA G-quartet – snall molecule interaction.

CARB 106

Biosynthesis of O-glycans and cost effective strategies for the synthesis of mucin O-glycans

Khushi L. Matta*, khushi.matta@roswellpark.org, Vipin Kumar, vipin.kumar@roswellpark.org, Siraj K Khaja, and Jun Xue, Cancer Biology,*

Roswell Park Cancer Institute, Elm & Carlton Streets, Buffalo, NY 14263, Fax: 716-845-8768

Interfacing between chemistry, biology and medicine is important in providing a valuable “tool-kit” for further understanding of biological systems at the molecular level. A basic carbohydrate from a natural source can act as an acceptor for two different enzymes capable of incorporating the same monosaccharide at two different positions in the acceptor. Chemical modification of the basic acceptor structure by introduction of O-Me or fluoro groups can result in highly specific acceptors, or inhibitors for individual glycosyltransferases. Synthetic acceptors can thus be used as a tool to study the biosynthesis of mucin O-glycans, as discussed in this presentation. For such studies, a cost effective strategy based on the use of Naphthylmethyl (Nap) function at the anomeric position of GalNAc and GlcNAc has been developed for the synthesis of selected glycan arrays of O-glycans. Galâ1,3GalNAca is a common structure in core 1 and core 2 O-linked mucin glycans whereas Galâ1,3GalNAcâ is prevalent in glycolipids. We have also made use of GalNAcâ-O-Nap glycosides as the precursor of both Galâ1,3GalNAca and Galâ1,3GalNAcb glycosyl donors. The scope of this strategy for the synthesis of glycan arrays for analysis of O-glycans will be discussed.

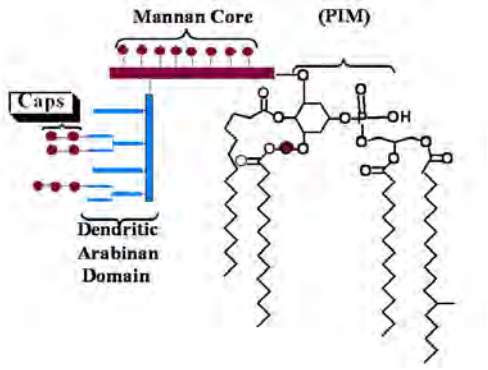
Supported by NIH grant R21 CA121294.

CARB 107

Developments in the total synthesis of M. tuberculosis LAM prototype

Bert Fraser-Reid*, dglucose@aol.com, Natural Products and Glycotechnology Research Institute, CiVentiChem, 595 F Weathers Field Rd, Pittsboro, NC 27312, Fax: 919-542-7111, Ramamurty VS. Changalvala, cvsrmurthy@yahoo.com, Natural Products and glycotechnology Reasearch institute, Civentichem,1001sheldon drive, suite:101, cary, NC 27153, and Siddhartha Ray Chaudhuri, sidhurc@yahoo.com, Natural Products and Glycotechnology Research Institute, CiVentiChem, 1001 Sheldon Dr, Cary, NC 27513*

The cartoon shows one of many representations of the immunomodulatory cell surface glycolipid, lipoarabinomannan (LAM), of mycobacteria. The structure is clearly divisible into several domains, each of which presents its own challenges for synthesis. Our efforts to cope with these challenges will be discussed.



CARB 108

Application of surface plasmon resonance (SPR) in glycobiology: Characterization of molecular interactions between GAGs and proteins

***Fuming Zhang**, zhangf2@rpi.edu, Department of Chemical and Biological Engineering, Rensselaer Polytechnic Institute, Center for Biotechnology and Interdisciplinary Studies, 110 8th Street, Troy, NY 12180, and Robert J Linhardt, linhar@rpi.edu, Departments of Chemistry and Chemical Biology, Rensselaer Polytechnic Institute, Center for Biotechnology and Interdisciplinary Studies, 110 8th Street, Troy, NY 12180*

Glycosaminoglycans (GAGs) are a family of highly sulfated, complex, polydisperse linear polysaccharides that display a variety of important biological roles. GAGs interact with many cationic proteins giving rise to myriad biological activities. Some of these interactions have received extensive attention in recent years, including heparin binding to growth factors influencing angiogenesis and other proliferation-dependent processes, and heparin binding to the ectodomain proteins of pathogens influencing infection. Surface plasmon resonance (SPR) spectroscopy has been successfully used for biophysical characterization of GAGs-protein interactions. In natural biological systems, most of GAGs are found attached on the cell surface through core proteins, and capture the target proteins that flow over the cell surface. Modeling this interaction by SPR is best be achieved by immobilizing GAGs on the surface of a biosensor chip. In the present study, we report SPR interaction studies on the interactions between GAGs and proteins, which include SDF-1 (stromal cell-derived factor-1), fibroblast growth factors and receptors (FGFs and FGFRs), proteins in Hedgehog Signaling Pathway, and virus envelope proteins and MMP-7 (Matrix metallopeptidase).

CARB 109

Caenorhabditis elegans bus-2 mutant reveals a new class of O-glycans involved in bacterial resistance

*Elizabeth Palaima[1], Catherine E. Costello[2], cecmsms@bu.edu, Jonathan Hodgkin[3], jonathan.hodgkin@bioch.ox.ac.uk, Maria Gravato-Nobre[3], Nancy Leymarie[4], and **John Cipollo**[5], john.cipollo@fda.hhs.gov. (1) Center for Biomedical Mass Spectrometry, Boston University School of Medicine, 670 Albany Street, Boston, MA 02118, Fax: 617-638-6761, (2) Center for Biomedical Mass Spectrometry, Boston University School of Medicine, 670 Albany Street, Rm 511, Boston, MA 02118, (3) Genetics Unit, Department of Biochemistry, University of Oxford, University of Oxford, South Parks Road, Oxford OX1 3QU, United Kingdom, (4) Department of Biochemistry, Center for Biomedical Mass Spectrometry, 670 Albany Street, Boston, MA 02118, (5) DBPAP, Food and Drug Administration CEnter for Biologics Evaluation and Research, 8800 Rockville Pike, Building 29 room 126, Bethesda, MD 20892, Fax: 301-402-2776*

Microbacterium nematophilum causes a non-lethal cutaneous infection of the C. elegans rectum and surrounding tissue. The M. nematophilum resistant bus-2 strains contain a genetic lesion in one of three core-1 galactosyltransferase homologues and are resistant to this infection. This situation implies that the infection requires the presence of host core-1 O-glycoconjugates. Here we use a series of mass spectrometry and chemical analyses, fluorescent protein expression and whole mount nematode staining and lectin procedures to reveal that indeed bus-2 is deficient in core-1 O-glycans in the region of infection. Also, these mutants reveal a new subclass of fucosyl O-glycans that contain internally linked GlcA. In the bus-2 genetic background core-1 glycans are decreased while the novel fucosyl O-glycans are increased in abundance in the region of infection. Our results suggest that this novel class of glycoconjugates may interfere or replace the natural M. nematophilum receptor, thus, leading to the resistance phenotype.

CARB 110

Dissecting the glycobiologic regulators of prostate tumor metastasis

***Charles J. Dimitroff**, cdimitroff@rics.bwh.harvard.edu, Department of Dermatology, Brigham and Women's Hospital, Harvard Medical School, HIM, Rm. 662, 77 Avenue Louis Pasteur, Boston, MA 02115, Fax: 617-525-5571*

Investigating the role of glycans and corresponding glycosyltransferase apparatus is broadening our understanding of the key pathologic mediators of prostate tumor metastasis. This research area has been fertilized by insights from the leukocyte homing paradigm, which has provided a platform of prospective glycobiological regulators of endothelial cell adhesion, trans-endothelial migration, and migratory activity in metastatic sites. To this end, we

modeled and considered known leukocyte-endothelial adhesion receptor - ligand pairs in the context of prostate tumor cell adhesion to vascular endothelium under physiologic blood flow conditions. Using state-of-the-art cell adhesion assays systems, we analyzed the adhesive properties of a number of prostate tumor cell lines expressing varying levels of alpha 2,3 sialylated – alpha1,3 fucosylated glycans. In blood flow, we found that sialyl LewisX-bearing glycoproteins on the surface of prostate tumor cells are key glycoconjugates that initiate cell binding to endothelial (E)-selectin on the vascular surface. Performance of RT-PCR on all putative glycosyltransferases involved in the synthesis of sialyl LewisX indicted that this prostate tumor cell binding property was due to elevated levels of alpha1,3 fucosyltransferases (FT) 3, 6 and 7. Moreover, elevations in FT3, FT6 and/or FT7 enzymes were also noted on native metastatic prostate tumor tissue from bone and liver when compared with levels found in localized prostate tumors or in normal prostate epithelia. These studies reveal and highlight the importance of the ‘hematopoietic mimicry' hypothesis in studying the trafficking mechanism of circulating prostate tumor cells into metastatic sites.

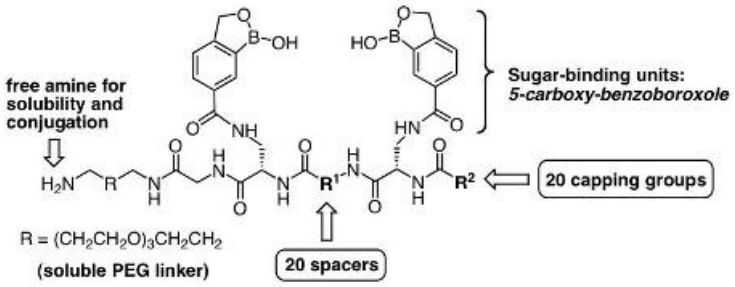
CARB 111

Design, synthesis, and screening of a library of peptidyl-oligo(boroxole) receptors for complex oligosaccharides in physiological conditions

***Arnab Pal**, arnab@ualberta.ca, University of Alberta, University of Alberta, Department of Chemistry, 11227 Saskatchewan Drive, Edmonton, Alberta T6G 2G2, Edmonton, AB T6G 2G2, Canada, Marie Bérubé, mberube@ualberta.ca, Department of Chemistry, University of Alberta, Edmonton, AB T6G 2G2, Canada, and Dennis G. Hall, dennis.hall@ualberta.ca, Department of Chemistry, University of Alberta, 11227 Saskatchewan Drive, Edmonton, AB T6G 2G2, Canada*

The ability of boronic acids to bind reversibly to simple carbohydrates in neutral water can be exploited to address the problem of cell-surface recognition. Recently, it has been shown that benzoboroxole can complex hexopyranosides under physiological conditions. [1] These hemiboronate units were essential to the design of a small library of well-defined peptidyl-diboroxole receptors for complex oligosaccharides. The library was synthesized using a combinatorial solid-phase approach with the Irori® technology, and it was screened in a biochemical assay for the selective recognition of the T-antigen disaccharide, a cancer-associated cell-surface marker. A few high-affinity receptors of low micromolar IC50 were identified, and their binding behavior in neutral water was characterized using competition experiments and a systematic evaluation of analogues. These results suggest that low molecular weight receptors for biologically relevant glycoconjugates could be made to rival the efficiency of

Nature's carbohydrate-binding proteins. References: [1] Dowlut, M.; Hall, D.G. J. Am. Chem. Soc. 2006, 128, 4226-4227.



CARB 112

Glycosignature analysis of complex carbohydrates

Sergei A. Svarovsky*, Sergei.Svarovsky@asu.edu, Center for Innovations in Medicine, Biodesign Institute at ASU, 1001 S McAllister Ave, Tempe, AZ 85287, Fax: 480-727-0782*

Glycans are important in most biological processes, yet their exact functions remain enigmatic due to lack of suitable tools for their analysis. Emerging technologies, such as glycan and lectin microarrays, are already transforming functional glycan analysis from one-at-a-time identification to an empirical pattern-recognition process. Here we introduce an alternative technology that is complementary to lectin microarrays, yet it does not suffer from restrictions imposed by the limited availability and specificity of natural lectins. The platform is based on a 3D bioaffinity matrix composed of a large number of imprinted peptides. Screening such a matrix with multivalent glycoconjugates reveals distinct binding patterns (glycosignatures) that can be used to distinguish one glycoconjugate from another. Using this technology we have been able to differentiate between isomeric oligosaccharides, protein glycoforms, and bacterial polysaccharides. These results suggest new opportunities for the analysis of other complex glycans that are unyielding to the existing analytical methods.

CARB 113

Click assisted synthesis of glycosulfopeptide mimetics of P-selectin glycoprotein ligand-1

Yusuf Vohra*[1], yusuf@uga.edu, Floris L. van Delft[2], and Geert Jan Boons[1], gjboons@ccrc.uga.edu. (1) Department of Chemistry, University of Georgia, Complex Carbohydrate Research Center, 315 Riverbend Road, Athens, GA*

30602, (2) Institute for Molecules and Materials, Radboud University Nijmegen, Heyendaalseweg 135, Nijmegen 6525 AJ, Netherlands

P-Selectin Glycoprotein Ligand-1 (PSGL-1), located on leukocytes, is a dimeric, mucin-type glycoprotein ligand known to play an important role in inflammation by binding to E-, P- and L-selectin. Inhibition of this binding by blocking PSGL-1 represents a promising therapeutic approach toward diseases in which inflammation has a destructive role (e.g. ischemia, venous thrombosis, hemorrhage, atherosclerosis, asthma, skin inflammation and autoimmune diseases). Glycosulfopeptides modeled on PSGL-1 have shown to inhibit P-selectin dependent leukocyte rolling in vivo in inflamed venules, suggesting that synthetic structures resembling the N-terminus of PSGL-1 represent a promising therapeutic target. A novel, highly convergent, completely synthetic route for the synthesis of glycosulfopeptide mimics of the signal sequence of PSGL-1 is presented for the first time. The method aims to provide sufficient quantities of the glycosulfopeptide for improved biological studies on the blocking of P-selectins and possible therapeutic use against chronic inflammation.

CARB 114

Solid-phase N-linked glycopeptide and glycoconjugate synthesis

Rui Chen, chenr@indiana.edu, Department of Chemistry, Indiana University, 800 E. Kirkwood Ave., Department of Chemistry, Bloomington, IN 47405-7102, Brian S. Hamilton, bshamilt@indiana.edu, Interdisciplinary Biochemistry Graduate Program, Indiana University, 800 E. Kirkwood Ave., Bloomington, IN 47405-7102, Junpeng Xiao, juxiao@indiana.edu, Interdisciplinary Biochemistry Graduate Program, Indiana University, Bloomington, IN 47405, Mark Pawlicki, Interdisciplinary Biochemistry Graduate Program, Indiana University, 800 E. Kirkwood Ave. Department of Chemistry, Bloomington, IN 47405-7102, and ***Thomas J Tolbert****, tolbert@indiana.edu, Department of Chemistry, Indiana University, 800 E. Kirkwood Ave., Bloomington, IN 47405*

N-linked glycopeptides and glycoconjugates can yield valuable information about the role of glycosylation in biochemical systems, but there are numerous obstacles to the synthesis of these compounds. N-linked oligosaccharides themselves are difficult to produce either by chemical synthesis or by isolation from natural sources and are therefore usually limiting reagents in the synthesis of N-linked glycopeptides or glycoconjugates. In addition, reactions coupling N-linked oligosaccharides to peptide acids can often be low yielding and prone to aspartimide formation. We have recently developed methods to produce relatively large amounts of N-linked oligosaccharides in glycosylation deficient yeast, and studies utilizing these high mannose oligosaccharides as starting materials for N-linked glycopeptide and glycoconjugate synthesis will be presented. Both on-resin coupling and glycosylated building block strategies to

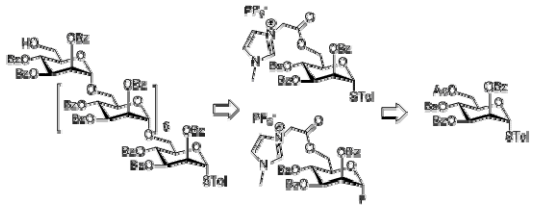
the synthesis of N-linked glycopeptides have been explored, and application of these techniques to the production of glycoconjugates and bioactive glycopeptides will be presented.

CARB 115

Imidazolium cation supported solution-phase synthesis of carbohydrates

***Ashish K. Pathak**, pathaka@sri.org, Division of Organic Chemistry, Southern Research Institute, 2000 Ninth Ave South, Birmingham, AL 35205, Fax: 205-581-2877*

Soluble imidazolium cations have recently been used as supports for catalyst/reagent immobilization and synthesis in homogeneous solution phase. The wide range of available imidazolium ionic liquid supports makes them compatible with most common chemical reactions. The solubility of imidazolium cation species can be turned on and off by variation of anions to make them phase separate from less polar organic solvents such as chloroform and aqueous media. Thus, imidazolium cation-supported species containing PF6- anion can be purified from the reaction mixture by simple washing with solvents such as diethylether and water. Herein, we report a successful orthogonal glycosylations of imidazolium supported thioglycoside and glycosyl fluoride to efficiently synthesize homo-linear oligosaccharide. This methodology provided homogeneous reaction conditions and eliminated the excessive use of column chromatography for the purification of products after each glycosylation step. All the IL supported glycosides were fully characterized by conventional NMR and MS spectroscopic techniques.



CARB 116

Kinetic and thermodynamic characterization of an enzyme that modifies the 2-deoxystreptamine ring common to all aminoglycoside antibiotics

***Adrianne L. Norris**, anorris7@utk.edu and Engin H. Serpersu, serpersu@utk.edu, Department of Biochemistry Cellular & Molecular Biology, The University of Tennessee, 1414 Cumberland Avenue, Knoxville, TN 37996-0840, Fax: 865-974-6306*

The aminoglycoside acetyltransferase (3)-IIIb (AAC), targets the deoxystreptamine ring that is common to all aminoglycoside antibiotics and modifies a large number of aminoglycosides. Kinetic studies have revealed that Km values fall within a small micro-molar range for aminoglycosides of varying size and structure. However, based on kcat/Km values, neomycins are more favored than kanamycins. Kinetic studies also yielded activation energies of 11.6 and 9.6 kcal/mol for the modification of kanamycin A and neomycin B, respectively. Isothermal titration calorimetry (ITC) experiments revealed that binding of aminoglycosides to AAC occurs with favorable enthalpy ($\Delta H<0$) and unfavorable entropy ($\Delta S<0$). The formation of ternary complexes is enthalpically more favored while entropically more disfavored compared to the formation of the respective binary complexes. Furthermore, a two-way synergistic effect has been observed for antibiotic and coenzyme binding. These results represent the first thermodynamic characterization of an aminoglycoside-modifying enzyme that modifies the 2-deoxystreptamine ring of aminoglycosides.

CARB 117

Modular synthesis of heparan sulfate fragments using orthogonally protected disaccharide building blocks

***Sailaja Arungundram**, sailaja@uga.edu, Department of Chemistry, Complex Carbohydrate Research Center, University of Georgia, 315, Riverbend Rd, Athens, GA 30602-4712, Fax: 706-542-4412, Kanar Al-Mafraji, kanar@ccrc.uga.edu, Complex Carbohydrate Research Center, University of Georgia, 315 Riverbend Rd, Athens, GA 30602, Jinkeng Asong, jinkeng@uga.edu, Complex Carbohydrate Research Center, University of Georgia, 315 Riverbend Road, Athens, GA 30602, Andre Venot, avenot@ccrc.uga.edu, Complex Carbohydrate Research Center, University of Georgia, 315, Riverbend Rd, Athens, GA 30602, and Geert-Jan Boons, gjboons@ccrc.uga.edu, Department of Chemistry, Complex Carbohydrate Research Center, University of Georgia, 315 Riverbend Road, Athens, GA 30602*

Heparan sulfate (HS) is a linear, polyanionic heavily *O*- and *N*- sulfated polysaccharide. HS-protein complexes mediate several biological processes such as homeostasis, growth-factor activity, anticoagulation, cell adhesion and enzyme regulation. The precise correlations between HS sequences, the sulfation patterns and binding to a given protein are mostly unknown. Recently, HS has been shown to inhibit Alzheimer's β-secretase (BACE-1, β-site amyloid precursor protein cleaving enzyme-1). BACE-1 cleaves the amyloid precursor protein (APP), which leads to the formation of aggregated amyloid β-peptide, a characteristic of Alzheimer's disease. Herein, we report a general modular approach for the efficient synthesis of a wide range of HS structures with diverse sulfation patterns. The synthesis of a library of tetrasaccharides modified at the positions of *O*-sulfation, *N*-acetylation, and *N*-sulfation using a set of orthogonally

protected disaccharide building blocks and a study of the binding affinities of these tetrasaccharides to BACE-1 will be presented.

CARB 118

Conformational analysis of nucleosides and nucleotides: An update of the PSEUROT program

Steven M. Graham*, grahams@stjohns.edu, Department of Chemistry, St. John's University, 8000 Utopia Parkway, Queens, NY 11439, Fax: (718) 990-1876*

The biological activity of nucleosides and nucleotides is intimately tied to their conformation equilibrium. Most nucleosides and nucleotides exhibit a two-state ‘north-south' equilibrium. In this formalism, ‘north' describes a nucleos(t)ide where C2' is puckered ‘down' and C3' is puckered ‘up'; ‘south' describes a nucleos(t)ide where C2' is puckered ‘up' and C3' is puckered ‘down'. The PSEUROT program allows a user to input ^{1}H-^{1}H coupling constants, obtained from NMR spectroscopy, and to obtain as output the ratio of north/south conformers that would have produced the observed coupling constants. The original PSEUROT program, to our knowledge, has not been updated in a systematic fashion in the 30 years subsequent to its first description. This talk will focus on the merits of the use of molecular mechanics (AMBER) methods versus *ab initio* methods to update the PSEUROT program.

CARB 119

Homo-C-nucleoside analogs III: Studies on the base catalyzed dehydrative cyclization of 4-(D-manno-pentitol-1-yl)-2-phenyl-2H-1,2,3-triazole

Mohammed AE. Sallam*, maesallam@yahoo.com, Chemistry Department, Chemistry Department, Faculty of Science, Alexandria University, Alexandria, Egypt, Alexandria, Egypt, Fax: 203 4812110*

Treatment of 4-(D-manno-pentitol-1-yl)-2-phenyl-2H-1,2,3-triazole 1 with one mole equivalent of p-toluenesulfonyl chloride in pyridine solution, afforded mono-partially substituted homo-C-nucleoside derivatives; 4-(2,5-anhydro-4x and 1x-p-toluenesulfonyl-D-manno-pentitol-1-yl)-2-phenyl-2H-1,2,3-triazoles. 4-(5x-O-p-toluenesulfonyl-D-manno-pentitol-1-yl)-2-phenyl-2H-1,2,3-triazole was isolated as an intermediate and 4-(5x-chloro-5-deoxy-D-manno-pentitol-1-yl)-2-phenyl-2H-

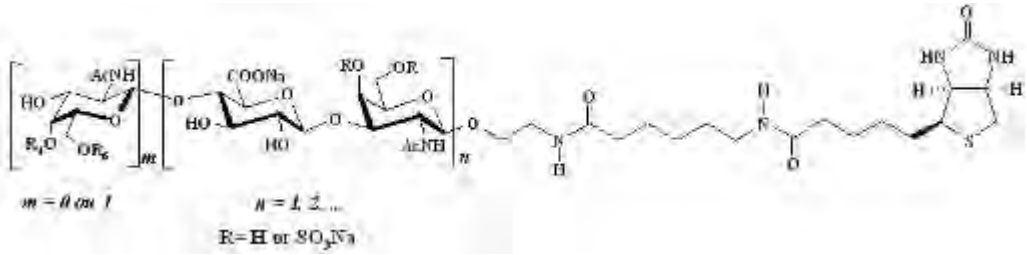
1,2,3-triazole, was isolated as a byproduct. Treatment of 1 with one mole equivalent of 2,4,6-triisopropylbenzenesulfonyl chloride (TIBSCl) afforded the parent homo-C-nucleoside analog 4-(2,5-anhydro-D-manno-pentitol-1-yl)-2-phenyl-2H-1,2,3-triazole in 54% yield and 4-(α-D-arabinopyranosyl)-2-phenyl-2H-1,2,3-triazole analog in 3% yield. The intermediate 5-triisopropylbenzenesulfonyl analog and the by product 5-chloro-5-deoxy analog, were also isolated from the reaction mixture. The mechanism of the reaction will be discussed. The structure of the products were determined by acylation, NMR, MS and CD spectroscopy.

CARB 120

Step economy process for the efficient and stereocontrolled construction of biotinylated chondroitin sulfate oligosaccharides

***Aude Vibert**, aude.vibert@univ-orleans.fr, ICOA-CNRS UMR 6005, University of Orléans, UFR Sciences, BP 6759, 45067 Orléans cedex 2, France, Fax: (+33)2 38 41 72 81, Chrystel Lopin-Bon, chrystel.lopin-bon@univ-orleans.fr, ICOA-CNRS UMR 6005, University of Orléans, UFR Sciences, BP 6759, 45067 Orléans Cedex, France, and Jean-Claude Jacquinet, jean-claude.jacquinet@univ-orleans.fr, ICOA -CNRS UMR 6005, University of Orléans, UFR Sciences BP 6759, 45067 Orléans cedex, France*

Osteoarthritis is the most frequent articular disease, but until now, no efficient treatment exists. This pathology is characterised by a cartilage's degeneration and a destruction of its components. One of the major components is chondroitin sulfate and we were interested in the study of their biosynthesis. A collection of biotinylated 4-sulfate or 6-sulfate chondroitin oligosaccharides and their non-sulfated analogues have been prepared in order to elucidate the substrate specificity of two types of enzymes implicated is this biosynthesis: chondroitin synthase and sulfotransferases. The first step of the synthesis is an acid hydrolysis of a polymeric chondroitin sulfate affording a basic chondroitin disaccharide unit. This key intermediate was used as starting material for the stereocontrolled synthesis of the biotinylated size-defined oligomers.



CARB 121

Studies of the racemization of Tn-antigen containing glycopeptides via solid-phase peptide synthesis

***Yalong Zhang**, zhangy7@mail.nih.gov, Laboratory of medicinal chemistry, National Cancer Institute, 376 Boyles street, Frederick, MD 21702*

The Tn antigen (GalNAcáSer/Thr) has been identified as tumor-associated carbohydrate antigen and cancer vaccines containing synthetic Tn glycopeptides have progressed into clinical trials. The property of peptides is critically dependent on the configuration of the chiral center. The alteration of a single chiral center can have a drastic change on immunogenic activities, resulting in an unfavorable immune response. Furthermore, it is extremely difficult to separate the unnatural enantiomers from the natural peptides. Therefore, racemization must be minimized during the peptides synthesis. However, little research has been done on the racemization of Tn during the solid-phase peptide synthesis. Preliminary studies in our group have shown that coupling of glycosylated amino acid using PyBOP/HOAT can produce as high as 11 % racemization, suggesting that a more in depth study should be carried out. Here, D- and L- Tn standards were synthesized and an HPLC assay was set up to measure racemization and yield for the solid phase synthesis FmocTn-Gly-Hex-OH using various coupling conditions.

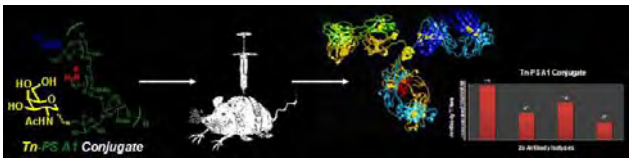
CARB 122

Immunological responses from an entirely carbohydrate antigen: Design of synthetic vaccines based on Tn-PS A1 conjugates

***Peter R. Andreana**, pra@chem.wayne.edu, Department of Chemistry, Wayne State University, 5101 Cass Ave, 335 Chemistry Building, Detroit, MI 48202, Fax: 313-577-7785*

Vaccines are powerful tools for disease prevention and various cell surface carbohydrates are important templates for their development. However, as isolated single entities carbohydrates have only been known to invoke T-cell-independent immune responses. To elicit a strong and long-term immunity, a vaccine must target the class II major histocompatibility complex (MHCII) and CD4+ T-cells in a T-cell-dependent cascade. Most recently zwitterionic polysaccharides were isolated from anaerobic bacteria and shown to modulate the cellular immune system by activating CD4+ T-cells via MHCII. Based on this discovery and as an alternative approach for vaccine development, we hypothesize that chemically conjugating tumor associating carbohydrate antigens/haptens (TACAs) to zwitterionic polysaccharides (ZPS) will lead to T-cell-dependent vaccines. This talk will focus on the isolation, purification, chemical modification of PS A1 (a naturally occurring capsular polysaccharide) and subsequent in vivo mouse studies with a carbohydrate cancer antigen (Tn)

conjugated to PS A1. The results will demonstrate that an IgG immune response is specific for Tn antigen highlighting an MHCII mediated immune response.



CARB 123

Functional glyco-capturing macroligand for glyco-proteomics and glycomics

***Xue-Long Sun**, x.sun55@csuohio.edu, Srinivas Chalagalla, and Satya Narla, Department of Chemistry, Cleveland State University, 2121 Euclid Avenue SI313, Cleveland, OH 44115*

Functional investigation of biomolecules typically starts by reducing the sample complexity through multidimensional separation methods based on the unique characteristics of the biomolecules followed by identification. We report here a chain-end functionalized glycopolymer and boronic acid-containing polymer (boropolymer) as oriented multivalent glyco-affinity capture ligands for efficient purification and identification of carbohydrates-binding proteins and carbohydrates and glycoconjugates. Briefly, chain-end glycopolymer and boropolymer were synthesized via arylamine initiated cyanoxyl-mediated free-radical polymerization in one-pot fashion. Oriented and covalent immobilization of chain-end functionalized glycopolymer and boropolymer onto solid surfaces, such as magnetic beads, mica, and glass slide were investigated and confirmed by fluorescent imaging and AFM techniques. In addition, glyco-affinity capturing and glyco-capture were demonstrated by using magnetic bead founctionalized with glycopolymer and boropolymer followed by mass spectrometry identification.

CARB 124

Novel glycan clusters as epitope mimics of the HIV-neutralizing antibody 2G12

***Lai-Xi Wang**, LWang3@ihv.umaryland.edu, Institute of Human Virology and Department of Biochemistry & Molecular Biology, University of Maryland School of Medicine, 725 West Lombard Street, Baltimore, MD 21201*

HIV-1 has evolved a number of mechanisms, including frequent mutations and heavy glycosylation, to evade immune responses. A dense array of immunologically “self” carbohydrates on the viral surface provides a strong

defense against host immune surveillance. Nonetheless, the discovery of a novel oligomannose glycan cluster on gp120 as the presumed epitope of the neutralizing antibody 2G12 has stimulated high enthusiasm in targeting HIV-1 carbohydrate antigens as a vaccine strategy. This presentation will cover our recent work on creating novel glycan clusters to mimic 2G12 epitope for vaccine design. These will include: 1) design and synthesis of template-assembled oligomannose clusters; 2) glycan clusters in the context of V3 domain; and 3) glycan clusters in the context of IgG-Fc fusion protein. The 2G12-binding studies and preliminary animal immunization with a glycoconjugate will be discussed.

CARB 125

Potent antiviral activity of the lectin griffithsin

Barry O'Keefe[1]*, okeefe@ncifcrf.gov, Barbara Giomarelli*[2]*, Carrie Saucedo*[2]*, Paul McCray*[3]*, Calli Lear*[4]*, Eugene Olinger*[4]*, Kenneth E. Palmer*[5]*, kenneth.palmer@louisville.edu, Robin Shattock*[6]*, and James B. McMahon*[2]*. (1) Molecular Targets Development Program, National Institutes of Health, NCI-Frederick, CCR, Bldg 562, Rm. 201, NCI-Frederick, Frederick, MD 21702, (2) Molecular Targets Development Program, National Institutes of Health, NCI-Frederick, CCR, Frederick, MD 21702, (3) Carver College of Medicine, University of Iowa, Ames, IA 52242, (4) Virology Division, United States Army Medical Research Institute of Infectious Diseases, Frederick, MD 21702, (5) Department of Pharmacology and Toxicology, University of Louisville, Kentucky, James Grahm Brown Cancer Research Center, 529 Jackson St, Louisville, KY 40202, (6) Centre for Infection, Division of Cellular & Molecular Medicine, St George's University of London, London, England*

The antiviral lectin griffithsin (GRFT), isolated from the red alga Griffithsia sp., is a 12.7 kDa protein originally identified based on its picomolar activity against HIV in cell-based in vitro assays. GRFT was found to have a unusual three-dimensional structure with three carbohydrate binding sites per monomer and to block viral fusion and entry. More recent studies have shown that GRFT can be manufactured on a large-scale by recombinant production in Nicotiana sp. This has allowed for a wider range of studies on this lectin. Since its discovery, GRFT has been tested for activity against a broad spectrum of viruses. Here we report recent progress on the development of GRFT for use as a systemic, topical and intranasal antiviral agent. Results from recent ex vivo and in vivo studies showing GRFT's activity against HIV, ebola Zaire and the SARS coronavirus will be presented.

CARB 126

Targeted antigen delivery using beta 1,3-glucan particles

Subhalakshmi Nagarajan[1]*, subha.nagarajan@umassmed.edu, Haibin Huang*[2]*, Ernesto Soto*[3]*, Stuart Levitz*[2]*, and Gary Ostroff*[3]*. (1) Program in Molecular Medicine, University of Massachusetts Medical School, 373 Plantation Street, Biotech 2 Suite 113, Worcester, MA 01605, Fax: 508-856-4289, (2) Department of Medicine, University of Massachusetts Medical School, 364 Plantation street, Worcester, MA 01605, (3) Program in Molecular Medicine, University of Massachusetts Medical School, 373 Plantation Street, Biotech 2, Suite 113, Worcester, MA 01604*

Many vaccines are poorly immunogenic necessitating the use of adjuvants and delivery systems to achieve strong and persistent immune responses. Here we report a novel combined adjuvant-delivery system based on β1,3-glucan particles (GP). GP are hollow, porous 2-4 micron microspheres useful for encapsulation and delivery of protein, DNA and siRNA to dendritic cells (DC). Ovalbumin (OVA) has been used as a model antigen to develop and optimize three different formulation strategies. Strategy 1 involved chemical coupling of fluorescently labeled OVA (fOVA) to the GP surface. Strategy 2 utilized electrostatic polyplex formation, and strategy 3 used heat denaturation to trap fOVA inside GP. The entrapment of fOVA within the GP was visualized by fluorescent microscopy and quantified by fluorescence spectroscopy. Encapsulation of electrostatically bound OVA inside GP resulted in 100-fold more efficient targeted delivery of OVA to DC *in vitro* compared to free OVA, and robust induction of humoral and T-cell responses *in vivo*.

CARB 127

Recent developments in pentenyl based glycosylations: Applications to biologically relevant oligosaccharides

J. Cristobal Lopez[1]*, clopez@iqog.csic.es, Ana M. Gomez*[2]*, Clara Uriel*[3]*, Juan A. Ventura*[3]*, and Bert Fraser-Reid*[4]*, dglucose@aol.com. (1) Department of Bioorganic Chemistry, Instituto de Quimica Organica General, Juan de la Cierva 3, 28006 Madrid, Spain, (2) Instituto de Quimica Organica General (CSIC), Juan de la Cierva 3, Madrid, Spain, (3) Instituto de Quimica Organica General, Juan de la Cierva 3, 28006 Madrid, (4) Natural Products and Glycotechnology Research Institute, CiVentiChem, 595 F Weathers Field Rd, Pittsboro, NC 27312*

During the last few years our research groups have been interested in the development of regioselective glycosylation protocols which would obviate tedious protection–deprotection steps.[2] These findings can be applied to the development of iterative glycosylation strategies with partially unprotected glycosyl donors [3]. We are currently applying these methods have been applied to synthetic strategies leading to biologically relevant oligosaccharides such as PI-88,[4] and some mannan portions of gp-120[5].

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CARB 128

1,5-C-Thio-sugars as selective inhibitors of thioredoxins

Zbigniew J. Witczak*, zbigniew.witczak@wilkes.edu, Dept.of Pharmaceutical Sciences, Wilkes University, School of Pharmacy, Wilkes-Barre, PA 18766, Fax: 570-408-7828*

The biological activities of thioredoxin reductase TRX and thioredoxins TX and their apparent relevance to aggressive tumor growth suggest that this system may be an attractive target for cancer therapy. Of currently available chemotherapeutics agents, cis platin may directly affect the TRX/TX system. Carmustine (BCNU) and other nitrosourea drugs and disulfides such PX-12 is well known inhibitors of TRX/TX system.

In our laboratory we have developed a newest coupling reaction of functionalized new class of reactive thiols derived from highly reactive enone 3 with reactive carbohydrate thiols 4a-c in the presence of a catalytic amount of piperidine or tetramethyl guanidine (TMG) in polar solvent systems MeCN, THF. The regiochemistry of the Michael addition steroselectively produced 1, 4 adducts 5a-c. These adducts 5a-c, upon the conventional oxidation under mild conditions (diluted hydrogen peroxide in acetone), affords disulfides 6a-c as newest candidates for inhibition study of TRX/TX system

This presentation will summarize recent developments in the biological and chemical functionalization of bioisosteres of new carbohydrate disulfide analogs, from three major carbohydrate families (L-arabinose, D-galactose and D-lactosamine). Progress toward the design and discovery of TRX/TX system specific inhibitors will be discussed as well.

CARB 129

Mechanism of cellulose hydrolysis by inverting GH8 endoglucanases: A QM/MM metadynamics study

Luis Petersen[1]*, lpm@iastate.edu, Albert Ardèvol*[2]*, aardevol@pcb.ub.es, Carme Rovira*[3]*, crovira@pcb.ub.es, and Peter J. Reilly*[1]*, reilly@iastate.edu. (1) Department of Chemical and Biological Engineering, Iowa State University, 2114 Sweeney Hall, Ames, IA 50011-2230, Fax: 515-294-2689, (2) Computer Simulation and Modeling Laboratory, Universitat de Barcelona, 08028 Barcelona, Spain, (3) Parc Científic de Barcelona, Josep Samitier 5, 08028 Barcelona, Spain*

Hydrolysis by *Clostridium thermocellum* endo-1,4-glucanase was computationally simulated with quantum mechanics/molecular mechanics metadynamics based on Density Functional Theory. Our calculations show that the glucosyl residue in subsite –1 in the Michaelis complex is in a distorted $^{2}S_{O}/^{2,5}B$ ring conformation, agreeing well with its crystal structure. In addition, our simulations capture the cationic oxacarbenium ion-like character of the TS, with a partially-formed double bond between the ring oxygen and C5' carbon atoms. The simulations clearly show for the first time in GH8 members that the TS features a boat-type conformation of the glucosyl unit in subsite –1. The overall catalytic mechanism follows a D_N*A_N-like mechanism and a beta-$^{2}S_{O}$ to $^{2,5}B$ [TS] to alpha-$^{5}S_{1}$ conformational itinerary along the reaction coordinate, consistent with the *anti*-periplanar lone pair hypothesis. Because of the structural similarities and sequence homology among all GH8 members, our results can be extended to all GH8 cellulases, xylanases, and other endoglucanases.

CARB 130

Molecular modeling of bacterial exopolysaccharides

Michelle M. Kuttel[1]*, mkuttel@cs.uct.ac.za, Roberto Rizzo*[2]*, rizzor@units.it, Paola Cescutti*[2]*, pcescutti@units.it, and Neil Ravenscroft*[3]*, neil.ravenscroft@uct.ac.za. (1) Department of Computer Science, University of Cape Town, Private Bag X3, Rondebosch, Cape Town 7701, South Africa, Fax: 27-21-6899465, (2) Department of Life Sciences, University of Trieste, via L. Giorgieri 1, Trieste I-34127, Italy, (3) Department of Chemistry, University of Cape Town, 7701 Rondebosch, South Africa*

Lung infections of Cystic Fibrosis patients are often associated with bacterial phenotypes which produce exopolysaccharides. These molecules play an important role in infection[1]. Due to their large size and component heterogeneity, the structural characterization of these molecules presents a number of challenges. Molecular modeling can potentially complement experiment in the determination of the preferred conformations of these molecules. We present computational investigations of the structure and dynamic behaviour of two exopolysaccahrides from a multi-resistant bacterium, *Inquilinus*

limosus, found to infect the respiratory tract of cystic fibrosis patients[2]: [3)-[4,6-O-(1-carboxyethylidene)]-β-D-Glcp(1→]n and [2)-[4,6-O-(1-carboxyethylidene)]-α-D-Manp(1→]n. The unusual complete pyruvate substitution on these molecules necessitated the extension of an existing carbohydrate force field with parameters for this group.

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CARB 131

Cryopreservation of primary hepatocytes using oligosaccharides

Yoshitaka Miyamoto*, miyamoto-y@ymail.plala.or.jp and Shin Enosawa, Department of Innovative Surgery, National Research Institute for Child Health and Development, 2-10-1, Okura, Setagaya-ku, Tokyo 157-8535, Japan, Fax: 81-3-3417-2864*

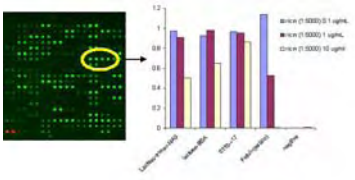
Human hepatocytes are valuable not only in biological but also pharmaceutical investigations because they are essential for preclinical testing of drug candidates. To freely and effectively utilize these cells, we aimed at improving cryopreservation techniques. However, the freeze-and-thaw process obviously damages cells. In particular, primary hepatocytes are one of the most difficult types of cells to cryopreserve. We investigate factors associated with successful hepatocyte cryopreservation, focusing on the effect of sugar molecule such as trehalose and related oligosaccharides. Addition of oligosaccharides with higher molecular weights in dimethylsulfoxide-base cryopreservation solution resulted in greatest improvement in cell viability. Moreover, attachment and survival rates in plastic dishes were approximately 1.2–1.8-fold greater after freezing in the presence of di-, tri-, and tetrasaccharides. Intrestingly, maltose showed rather better potency of the improvement than trehalose in cell survival. In conclusion, oligosaccharides were effective on the viability and survival of cryopreserved hepatocytes.

CARB 132

An array-based method to identify high affinity inhibitors for carbohydrate-binding proteins

***Yalong Zhang**, zhangy7@mail.nih.gov, Laboratory of medicinal chemistry, National Cancer Institute, 376 Boyles street, Frederick, MD 21702*

Understanding and evaluating interactions between carbohydrates and proteins is import for applying glycoconjugates as diagnostic and therapeutic agents. Identification of high affinity ligands is difficult for several reasons. First, traditional methods used to measure binding can only test a limited number of oligosaccharides and may fail to find the highest affinity ligands. Second, the design of multivalent ligands is complicated because of the importance of ligand spacing, orientation, and density. Therefore, aggregate formation in many assays on the surface of the plate is difficult to distinguish with the preferred one to one binding. Our group has been developing carbohydrate array technology. A new method is applied by exploring mixing unmodified BSA with neoglycoconjugates to space the neoglycoconjugates apart on the array surface. This is useful for achieving one to one binding and mimics the binding pattern in solution, which gives better evaluation of neoglycoconjugates as inhibitors in solution. As an initial test, we are evaluating several plant lectins including Concanavalin A (Con A), Vicia villosa lectin (VVL), Soybean agglutinin (SBA) and Ricinus communis agglutinin (RCA). It was found that glycoconjugates with a low affinity (higher IC50 value) gave significant decrease in the apparent binding constant with a decrease of glycoconjugates content on the array.The strategy is also being applied to ricin, a plant toxin classified as a level B biothreat by the CDC. High affinity, selective inhibitors of ricin could be used as potential anti-adhesion drug against the toxin. Currently, asialo fetuin was found to be strongest inhibitor with IC50 of 73 nM against ricin B chain, the lectin part of the toxin to initiate the invasion into cells.



CARB 133

Analysis of protein glycation using phenylboronate acrylamide gel electrophoresis

*Marta P Pereira Morais[1], M.P.Pereira.Morais@bath.ac.uk, Julia D Mackay[1], J.Mackay@bath.ac.uk, **Tony D. James**[2], T.D.James@bath.ac.uk, John S Fossey[3], J.S.Fossey@bham.ac.uk, and Jean M van den Elsen[1], J.M.H.V.Elsen@bath.ac.uk. (1) Department of Biology and Biochemistry, Univerity of Bath, Bath BA2 7AY, United Kingdom, (2) Department of Chemistry,*

University of Bath, Claverton Down, Bath BA2 7AY, United Kingdom, (3) School of Chemistry, University of Birmingham, Edgbaston, Birmingham B15 2TT, United Kingdom

Non-enzymatic glycosylation or glycation adversely affects protein structure, function and stability. Glycated substances are removed slowly from the body and accumulation of advance glycation endproducts (AGEs) have been implicated in many age-related chronic diseases. Incorporation of a specialized carbohydrate affinity ligand into polyacrylamide gels for SDS-PAGE make it possible to separate carbohydrates.(1) In this presentation we will show how this method has been adapted for the analysis of post-translationally modified proteins. We believe that this method will become an important new proteomics tool for the detection, separation, visualisation and identification of protein glycation.

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CARB 134

Redesigning the biological activities of heparan sulfate on a microfluidic chip

Jeffrey G. Martin[1]*, martij11@rpi.edu, Yongmei Xu*[2]*, William Gressick*[3]*, Zhenqing Zhang*[4]*, zhangz5@RPI.EDU, Wenjing Zhao*[5]*, zhaow4@rpi.edu, Renuka Bhisetti*[6]*, Priscilla Paul*[7]*, Fuming Zhang*[8]*, zhangf2@rpi.edu, Jian Liu*[9]*, liuj@email.unc.edu, Jonathan S Dordick*[7]*, dordick@rpi.edu, and Robert J Linhardt*[10]*, linhar@rpi.edu. (1) Departments of Chemistry and Chemical Biology, Rensselaer Polytechnic Institute, Biotech Center 4005, 110 8th Street, Troy, NY 12180, (2) Division of Medicinal Chemistry and Natural Products, University of North Carolina, Chapel Hill, NC 27599, (3) Center for Automation Technologies and Systems, Rensselaer Polytechnic Institute, 110 8th Street, Troy, NY 12180, (4) Department of Chemistry, Rensselaer Polytechnic Institute, Troy, NY 12180, (5) Department of Biology, Rensselaer Polytechnic Institute, 110 8th Street, Troy, NY 12180, (6) Department of Biology, Rensselaer Polytechnic Institute, Biotech Center 4005, 110 8th Street, Troy, NY 12180, (7) Dept. of Chemical & Biological Engineering, Rensselaer Polytechnic Institute, Troy, NY 12180, (8) Department of Chemical and Biological Engineering, Rensselaer Polytechnic Institute, Center for Biotechnology and Interdisciplinary Studies, 110 8th Street, Troy, NY 12180, (9) Division of Medicinal Chemistry and Natural Products, University of North Carolina, Chapel Hil, NC 27599, (10) Departments of Chemistry and Chemical Biology, Rensselaer Polytechnic Institute, Center for Biotechnology and Interdisciplinary Studies, 110 8th Street, Troy, NY 12180*

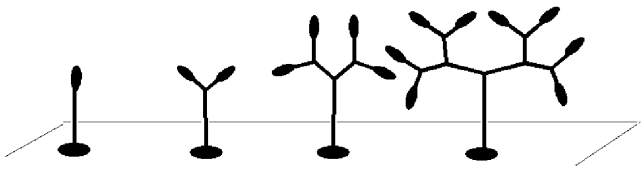
Using microfluidics, recombinant enzyme technology, and magnetic nanoparticles we have enzymatically modified heparan sulfate (HS) glycosaminoglycan chains immobilized on magnetic nanoparticles. Sulfo groups were transferred from adenosine 3'-phosphate 5'-phosphosulfate (PAPS) to the 3-hydroxyl group of the D-glucosamine residue in an immobilized HS chain using D-glucosaminyl 3-O-sulfotransferase. After modification, the nanoparticles with immobilized HS exhibited increased affinity for fluorescently labeled antithrombin III as detected by confocal microscopy. Since the biosynthesis of HS involves an array of specialized glycosyl transferases, epimerases, and sulfotransferases, this approach should mimic the synthesis of HS in vivo. Further, our method demonstrates the feasibility of investigating the effects of multi-enzyme systems on the structure of final glycan products for HS-based glycomic studies.

CARB 135

Detecting multivalency effects with glycodendrimers on microarray chips

Roland J. Pieters[1]*, r.j.pieters@uu.nl, Hilbert M. Branderhorst*[1]*, Nuria Parera Pera*[1]*, Raymond Kooij*[1]*, Rob. M. J. Liskamp*[1]*, and Rob Ruijtenbeek*[2]*. (1) Department of Medicinal Chemistry and Chemical Biology, Utrecht University, P.O.Box 80082, 3508 TB Utrecht, Netherlands, Fax: +31-30-253 6655, (2) Pamgene International B.V, P.O. Box 1335, 's Hertogenbosch 5200 BJ, Netherlands*

Protein-carbohydrate interactions are important in many biological processes, both normal and pathological. There is great potential for new drugs and diagnostic tools based on these interactions. Unfortunately, the weak binding of carbohydrate is often a problem. In nature, high affinities are attained by simultaneous binding of multiple sugars to multiple protein binding sites, i.e. multivalency. To discover mores cases of multivalency effects, we now increased the efficiency by using glycodendrimers on a micorarray surface, which allows a rapid screening and uses little material. Further advantages of the chips we use include on-line monitoring of binding and the high capacity and thus stronger signals since the chips are made of a porous 3D material. Several sugars were linked to the dendrimers and valencies of up to 8 were prepared and displayed on a microarray. The screening results of a number of carbohydrate binding proteins will be discussed



CARB 136

Structure and dynamics of sucrose in aqueous solution by computer experiments

***Junchao Xia**, junchao-xia@biomaps.rutgers.edu, BioMaPS Institute, Rutgers University, 610 Taylor Road, Piscataway, NJ 08854, and David Case, case@biomaps.rutgers.edu, Biomaps Institute, Rutgers University, 610 Taylor Rd, Piscataway, NJ 08854*

Sucrose, a simple disaccharide, is one of the most common sugars in our routine life. Although its crystal structure was solved more than 30 years ago, its conformation in aqueous solution is still a matter of debate. Solution experimental data have been measured using different techniques and in various conditions such as temperature, concentration, and solvent type. We report here computer experiments to reproduce these conditions via AMBER molecular dynamics simulations, and analyze NMR quantities including nuclear Overhauser effects, residual dipolar couplings and relaxation parameters (R1/R2) from the simulation trajectories. Our results show that sucrose is indeed a dynamic molecule, but the that crystal conformation is qualitatively the dominant one under most solution conditions.