



- **Extramural Service**

2006 to present	Editorial Board, <i>Organic Reactions</i>
2003 to present	Associate Editor, <i>Journal of Organic Chemistry</i>
1998-2006	Editorial Board, <i>Carbohydrate Research</i>
1998-2006	Editorial Board, <i>Journal of Carbohydrate Chemistry</i>
2005	Principal Investigator, National Science Foundation, Molecular Basis of Life Processes Workshop.
2002-2005	Principal Investigator, National Science Foundation, Physical Organic Workshop
2001 to 2005	Member, NIH MedChemA Study Section
2001	Ad Hoc Member of NIH, FIRCA Study Section
1999	Ad-Hoc Member of NIH, BNP Study Section
1998 to present	ACS, Carbohydrate Division, Member of the Executive Committee
1997	Faculty Mentor, Professional Internship Program
1995-96	Middle School Science Fair Mentor
1995-97	Joint Teaching Project with Community High School Teachers
1995	Chair, Southern Arizona Section of the American Chemical Society
1995	The University of Arizona Hillel Board Member
1995	The University of Arizona Science Teachers Colloquium Series Speaker
1994	Chair Elect, Southern Arizona Section of the ACS
1993	Treasurer, Southern Arizona Section of the ACS
1992	Treasurer, Southern Arizona Section of the ACS
1992	Faculty Mentor Professional Internship Program

*Proposal Reviewer*

National Institutes of Health

National Science Foundation

Petroleum Research Foundation

Research Corporation

Welcome, UK

Science Foundation of Ireland

*Publication Reviewer*

*Journal of the American Chemical Society*

*Angewandte Chemie*

*ChemMedChem*

*Organic Letters*

*Tetrahedron Letters*

*Journal of the Chemical Society, Perkin Transactions I*

*Bioorganic and Medicinal Chemistry Letters*

*Journal of Organic Chemistry*

*Carbohydrate Research*

*Tetrahedron*

*Journal of Magnetic Resonance*

*Chemtracts*

• **Publications**

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2. **1989** M.E. Jung and J. Gervay "Solvent Effects in Intramolecular Diels-Alder Reactions of 2-Furfuryl Methyl Fumarates: Evidence for a Polar Transition State" *J. Am. Chem. Soc.*, 111, 5469.
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11. **1995** Gy. Batta and J. Gervay "Solution-Phase  $^{13}\text{C}$  and  $^1\text{H}$  Chemical Shift Anisotropy of Sialic Acid and Its Homopolymer (Colominic Acid) from Cross-Correlated Relaxation" *J. Am. Chem. Soc.*, *117*, 368.
12. **1995** S.J. Danishefsky, J. Gervay, J.M. Peterson, F.E. McDonald, K. Koseki; D.A. Griffith; T. Oriyama; and S.P. Marsden "Application of Glycals to the Synthesis of Oligosaccharides: Convergent Total Syntheses of the Lewis X Trisaccharide Sialyl Lewis X Antigenic Determinant and Higher Congeners" *J. Am. Chem. Soc.*, *117*., 1940.

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18. **1997** A.L. Parrill and J. Gervay "Fostering Curiosity-Driven Learning Through Interactive Multimedia Representations of Biological Molecules." *J. Chem. Ed.*, *74*,1141.
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20. **1997** J. Gervay, T.M. Flaherty, C. Nguyen "Solution Phase Synthesis of (1 $\rightarrow$ 5)-Amide Linked Sugar Amino Acids Derived from Sialic Acids" *Tetrahedron Lett.*, *38*, 1493.
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22. **1997** J. Gervay, T. Nguyen, and M.J. Hadd "Mechanistic Studies on the Stereoselective Synthesis of Glycosyl Iodides: First Characterization of  $\beta$ -Glycosyl Iodides" *Carbohydr. Res.*, *300*, 119.
23. **1997** A.L. Parrill, N. Mamuya, D.P. Dolata, and J. Gervay "Computational Studies of Sialyllactones: Methods and Uses" *Glycoconj.*, *14*, 523.
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76. **2007** El-Badri, M.H., D. Willenbring, D.J. Tantillo, and J. Gervay-Hague "Mechanistic Studies on the Stereoselective Formation of  $\beta$ -Mannosides from Mannosyl Iodides Using  $\alpha$ -Deuterium Kinetic Isotope Effects" *J. Org. Chem.*, *72*, 4663-4672.
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3. **2003** J. Gervay-Hague "Preparation and Use of Gold Glyconanoparticles" Provisional Application Serial No. 60/475,836. Filed on June 3, 2003.
4. **2004** J. Gervay-Hague and L. Ying "Labeled Substrate Conjugates for Identifying Enzyme Inhibitors" Provisional Application Serial No. 60/591,414.
5. **2005** J. Gervay-Hague and W. Du "Highly efficient synthesis of alpha-O-Galactosyl Ceramides" US Serial No.: 60/658,936; UC Ref 2005-387-26.
6. **2006** J. Gervay-Hague, W. Du, A. Natarajan, S. DeNardo "Construction of Multivalent Antibody scFv Through Cu(I) Catalyzed 1,3-Dipolar Cycloaddition" Provisional UC Case NO. 2006-340.
7. **2006** J. Gervay-Hague, T. W. North, D. C. Meadows, Y. T. Duong "Synthesis, Mechanistic Studies, and Anti-HIV Properties of Potent Geminal Disulfone-Containing Compounds: Identification of a Coreceptor-Independent Small Molecule Inhibitor of Viral Entry" UC Case NO. 2006-248-1.
8. **2008** J. Gervay-Hague, Wenjun Du, Suvarn Kulkarni, and Matthew Schombs "One-pot Synthesis of unprotected  $\alpha/\beta$ -O-glycolipids"

- **Theses and Dissertations by Students Under Professor Gervay-Hague's Direction:**

1. Abigail L. Parrill, M.S. 1996 "Supplementing Traditional Chemical Education in the World Wide Web"

2. Nellie N. Mamuya, M.S. 1996 "Synthesis and NMR Studies of Neuraminidase Inhibitors"
3. Abigail L. Parrill, Ph.D., 1996 "Applications of Artificial Intelligence in Drug Design"
4. Terrence M. Flaherty, Ph.D., 1997 "1. Synthesis of C-Glycoside Sulfones via Oxirane-Thiirane Exchange. 2. Preparation of Sialic Acid Derivatives Amenable to Solid Phase Synthesis. 3. Conformational Analysis of Complex Polysaccharides"
5. Truc N. Nguyen, M.S. 1997 "1. Mechanistic Studies on the Formation of Glycosyl Iodides. 2. Synthesis of Amino Sugars via Glycosyl Iodides"
6. Can P. Nguyen, M.S. 1998 "Solution and Solid-Phase Synthesis of Sialooligomers"
7. Michael J. Hadd, Ph.D., 1998 "1. Anionic Additions to Glycosyl Iodides. 2. Neutral Addition of Alcohols to Glycosyl Iodides. 3. Glycosyl Iodides in Solid Phase Oligosaccharide Synthesis"
8. Nathan E. Stott, B.S. with Honors 1998 "Approaches to the Preparation of Psychosine Functionalized Polyamide Dendrimers with Buckminsterfullerene Cores"
9. Olivia E. Oehrle-Steele, B.S. with honors, 1999 "Use of ELISA to Investigate pH-Dependent Interactions Between Antibodies to *Neisseria Meningitidis* Strain B and Membrane Bound Colominic Acid"
10. Katherine D. McReynolds, Ph.D., 1999 "1. Development of a Novel Elisa for the Testing of Glycobiocjugates as Anti-HIV Agents. 2. Synthesis of Potential Inhibitors of the HIV Entry Mechanism. 3. Probing the Secondary Structural Characteristics of Oligosaccharides Utilizing Circular Dichroism"
11. Denise M. Scofield, M.S. 1999 "Synthesis of Non-Natural Carbohydrate-Based Ligands Designed to Bind HIV Gp120"
12. Son N. Lam, M.S. 2000 "Glycosylations via In Situ Formation of Glycosyl Iodides from Glycosyl Bromides"
13. Travis Q. Gregar, Ph.D., 2001 "Synthesis and Structural Characterization of Amide-Linked Neuraminic Acid Derivatives"
14. Son N. Lam, Ph.D., 2003 "Glycosyl iodides: A modern tool for Oligosaccharide Synthesis"
15. Laiqiang Ying, Ph.D., 2004 "I. Synthesis of Carbohydrate-Derived Building Blocks. II. Construction of Combinatorial and Parallel Libraries. III. Development of Fluorogenic Substrates for High-throughput Screening"
16. Jessica Wong, M.S. 2004 "Synthesis of Transition-State Analogs of GDP-Fucose as Glycosyl Transferase Inhibitors"

17. D. Christopher Meadows, Ph.D., 2005 “Design Synthesis and HIV Activity of Geminal Disphosphate-containing Compounds”
18. Yan Lu, M.S. 2005 “Synthesis of Neuraminidase Inhibitors Using Click Chemistry”
19. Wenjun Du, Ph.D., 2006 “Stereoselective Synthesis of  $\alpha$  *O*-Galactolipids and Construction of Di-ScFv through a Trialkyne-Azide 1,3-Dipolar Cycloaddition”
20. Mohamed El-Badri, Ph.D., 2007 “Synthetic and Physical Organic Studies of Stereoselective Glycosylation Reactions Using Glycosyl Iodides”
21. Urvashi Sahni, Ph.D., 2009 “Synthesis of Disulfone Analogs of Glycosyltransferases as Chemotherapeutic Agents”
22. Jonel P. Saludes, Ph.D., 2009 “Synthesis, Structural Characterization, Conformational Analysis and Plasma Stability Studies of Alpha/Delta-Hybrid Peptides Derived from 2,3-Dehydroneuraminic Acid and Glutamic Acids”

- **Research Accomplishments**

Our research team has established an internationally recognized program in the area of organic synthesis directed toward the design and synthesis of chemotherapeutics targeting HIV infection and cancer. Although the disease states differ, our method of drug development has consistently involved understanding disease processes at a molecular level so that rational drug design can be implemented. This approach has led us to studies at the interface of chemistry, biology, and virology. Our work is characterized by a total approach to drug design and synthesis that utilizes a wide variety of experimental tools available to chemists and biologists.

Synthetic expertise has been our most important contribution, allowing us to prepare compounds that uniquely serve as biological probes for structure/activity relationship (SAR) studies (**pubs 35, 36, 39, 43, 44, 46, and 49**). For several years, our efforts have concentrated on the design and synthesis of HIV/Host cell entry inhibitors based upon the galactosyl ceramide ( $\beta$ -GalCer) recognition element. HIV gains entry into T-cells through a process that begins with HIV-associated glycoprotein (gp120) recognition of a critical domain (CD4) on the host cell. Following this event, gp120 binds a chemokine co-receptor. This interaction leads to unmasking of the viral fusion domain, which initiates viral entry into the host cell. HIV is also capable of infecting cells that do not express CD4 through an alternate pathway involving recognition of a cell surface glycosphingolipid known as GalCer. The CD4, chemokine co-receptor, and GalCer

binding sites on gp120 are unique and each offers a target of opportunity for chemotherapeutic intervention. The GalCer site is of particular interest, since it may provide a means of delivering compounds to the surface of HIV that could prevent recognition of the chemokine co-receptor site, and consequently inhibit viral fusion with host cells.

We have focused on the identification of non-natural GalCer analogs that could serve as alternate ligands for gp120. Rapid screening biological assays have also been developed in my laboratory to support SAR studies (**pubs 35, 36, 43, 44, 49, WCT patent application 10/860,390**). We have quantitatively measured interactions between the viral surface protein and host cell carbohydrate ligands for the first time. These measurements have provided valuable insight into targeted recognition processes and have facilitated identification of lead drug candidates. GalCer analog syntheses have allowed the importance of both the lipid component and the carbohydrate to be studied. We have shown that the ceramide portion, which possesses two stereo centers, can be replaced with a readily available fatty acid (palmitic acid). This advancement has facilitated large-scale production of analogs, which is necessary for biological studies. The carbohydrate functionality has been probed to determine how modifications at specific sites alter the binding event. SAR and biological assay studies have indicated that several different carbohydrate head groups are tolerated. The finding that gp120 recognizes cellobiose to the same extent as galactose was especially significant because humans are unable to metabolize cellobiose, and it is not a natural cellular component.

The long-term goal of our HIV-research program has been the development of drug delivery systems that specifically interact with gp120. We have designed systems capable of presenting multiple ligands in defined geometries to this protein target (**pub 62, 72, 80**). Our working hypothesis has been that multiple binding events will make the interactions irreversible, and proper ligand placement will afford target specificity. As a part of this program, we have established solid-phase protocols for the synthesis of carbohydrate libraries derived from amide-linked sugar amino acid equivalents (**pubs 20, 24, 26, 28, 40, 48, 51, 52**). We have also developed new NMR experiments, which in combination with circular dichroism (**pub 38**) and computational studies (**pub 23**) have enabled the solution phase conformations of these compounds to be defined (**pubs 9, 10, 11, 13, 19, 21, 83, 94, 95, 96**). These combined efforts have produced novel materials with stable secondary structures in water. Moreover, we have

demonstrated that these unique molecular scaffolds resist adsorption of gp120 making them useful core structures for macromolecular assembly of rigid ligand arrays.

Recently we have expanded our glycolipid studies to include the synthesis of  $\alpha$ -GalCer analogs (**pub. 56, 70, 76, 77, 84, 88, 91**) These compounds mediate chemokine production in immune response and play important roles in cancer progression and anti-inflammatory response. The discovery that bacterial derived glycolipids can illicit an immune response has led to tremendous excitement in glycolipid research. Numerous labs all over the world are studying the molecular mechanisms of glycolipid biology. We have established fruitful collaborations with Professors Randy Brutkiewicz (Indiana University Cancer Center), which focus on understanding how  $\alpha$ -GalCer analogs mediate the immune response. Access to  $\alpha$ -GalCer analogs has allowed Professor Brutkiewicz to identify other bacterial derived ligands that illicit immune response (**pubs. 58, 63, 65, 66, 69, 73, 81, 85, 86, 92, 93**).

Our interests have also been directed to the synthesis of glycosyl transferase inhibitors designed to prevent expression of cell surface carbohydrates implicated in cancer (**pubs 25, 41, 78, 79, 82, 90, 97**). Sialyl Lewis X is a cell surface glycoconjugate that serves as a recognition element in tumor metastasis. It is a tetrasaccharide consisting of *N*-acetyl neuraminic acid (NeuAc)  $\alpha$ -(2 $\rightarrow$ 3) linked to galactose, which in turn is  $\beta$ -(1 $\rightarrow$ 4) linked to glucosamine bearing an  $\alpha$ -(1 $\rightarrow$ 3) linked L-fucose residue. Increased expression of Sialyl Lewis X correlates with high metastatic potential of cancer cells, and malignant cell invasions are inhibited by decreased expression of fucose in cell surface carbohydrates. There is abundant evidence linking sialyl and fucosyl transferase enzymes to both metastatic potential and patient survival making these enzymes key targets for chemotherapeutic intervention. The goal of our research has been to identify lead drug candidates that will inhibit these enzymes and act to slow or stop cancer metastasis. As a first step we have developed novel screening methods for rapid detection of potential inhibitors (Provisional Application Serial No. **60/591,414**)

We have developed three unique methods for the synthesis of a new class of compounds having the general structure sugar-CH<sub>2</sub>-SO<sub>2</sub>-CH<sub>2</sub>-X that are expected to mimic natural substrates having the general structure sugar-O-PO<sub>2</sub>-O-X. Reactions of exocyclic glycols with thiol acetic acid under radical conditions provide equatorially displaced *C*-glycoside thiols that have been further elaborated to *C*-glycoside sulfones. Axially displaced *C*-glycosides have been stereo specifically prepared from reactions of glycosyl iodides with suitable acceptor molecules (**pubs**

**22, 27, 31, 37**). The use of glycosyl iodides in organic synthesis is a proud accomplishment of our research team (**45, 47, 50, 53, 55, 60, 61**). Before our contributions, there was an existing folklore that glycosyl iodides were not suitable donors. Contrary to that belief, our work has demonstrated that glycosyl iodides are uniquely disposed to highly selective glycosylations leading to efficient syntheses of *C*, *N*, and *O*-glycosides (**pub 27**). More recently, we have achieved convergent syntheses of target compounds utilizing novel bis-sulfone bis-phosphonate reagents developed in our laboratory (**pub 41, US patents 6,812,365; B2, 6,498,277 B1**). These endeavors have provided highly efficient routes into biologically relevant sulfone analogs with potent anti-HIV activity (**pubs 57, 67, 68, 64, 71, 74, 75, 89**). This study actually began as a model study to determine the reactivity of the bis-phosphonate reagents, but serendipity took flight and several of the model compounds showed potent HIV-integrase activity. With these promising results, we have expanded the program to include SAR studies that have identified a new class of HIV-entry inhibitor as well. These studies have greatly benefited from collaborations with Professor Thomas North in the UC, Davis school of comparative medicine.