Description of Workshop:

The "lock and key" concept introduced into biochemistry by Emil Fisher over a century ago has now been reified by proteins (lectins) which are specific recognition molecules for highly ordered sugar multimers (glycans). This permits the large array of interactions seen in morphogenesis and immunology. Glycans formed from complex arrays of sugars thus constitute a language for multicellular biology that some have designated as 'third language of life and morphogenesis.' The past fifty years have witnessed a substantive and growing field of structural analysis and sequencing of glycans as well as chemical and enzymatic synthesis of these molecules. The time is at hand for the emergence of a theoretical glycobiology and search for the third language.
The central dogma of molecular biology describes DNA, RNA and proteins as the key molecules in biological information flow. It tends to ignore other essential biomolecules including glycans (multimers, oligomers, or polymers of sugars) that are the most plentiful molecules on the planet in terms of mass. Every cell is covered with glycans and most of the secreted proteins in higher organisms are glycosylated. In the latter half of the last century significant progress was made in genomic and proteomic sciences yielding the sequencing of genomes and proteomes of several organisms. However, this information alone has been unable to decipher and define the complexity of multicellular life. In the past decade, glycans have received more attention because of their universal presence in biological systems and their involvement in intermolecular and intercellular communication in almost all biological/physiological processes including morphogenesis, immune regulation and diseases such as cancer, inflammation and microbial infections.

Glycans are found in every organism and are used as energy production and storage molecules (glucose, starch, glycogen) and structural molecules (cellulose, peptidoglycans and proteoglycans) by all life forms. In addition, because of their structural diversity, they also act as key information molecules and chemical messengers (glycoconjugates and lectin receptors). There are four nucleotides and twenty amino acid monomers that form all known nucleic acids and proteins, respectively, seen in living organisms. On the other hand, the total number of sugar monomers (which can exist from three-carbon to nine-carbon forms) in living organisms is much larger. Unlike nucleic acids and proteins, sugars are polyfunctional. Therefore, glycans can polymerize in branched as well as linear fashion at a number of

linkage positions with different geometries, endowing them with significant complexity and with higher level of structural, functional and informational sophistication and flexibility. Sugars are indirectly controlled by the genome because the monosaccharide diversity is due to conversions mediated by enzymes, which are gene products. These glycans can exist in free form, conjugated to secondary metabolites or to proteins and lipids - conferring distinct and often crucial structural and functional properties. The number and structural diversity of sugars (and their polymers) greatly vary with evolutionary scale (i.e., the pool of monosaccharides and their oligomeric forms are overlapping with several distinct sugars).

In the unicellular organisms, the glycans predominantly play structural roles (in the form of peptidoglycans and cell walls) protecting them from environmental stresses (chemical and physical). However, glycans are also the key determinants of multicellularity and morphogenesis, being a major class of molecules that distinguishes prokaryotes and eukaryotes. Glycans cover the extracellular matrix of every cell and therefore are the chemical keys that carry the information required for regulated intercellular interactions at the cell surface level. Glycans from one cell bind to corresponding glycan-binding proteins (called lectins) on the interacting cells. This newer version of lock-and-key paradigm can be considered as a highly complex 'Velcro,' where several different shapes and sizes of complementary molecules interact to exchange chemical messages. It is likely that with the origin of multicellularity and morphogenesis, the need for complex intercellular (and intermolecular) communication arose which was accomplished by covalently conjugating glycans to proteins and lipids on the cell surface and on secreted molecules.

From the point of view of the chemical evolution of function it should be noted that glycans are made of monosaccharides derived from the core metabolites: glucose fructose, and ribose. In addition, synthesis of glycoconjugates requires activated sugar nucleotides using the same purines and pyrimidines found in RNA, again going back to core metabolism. Thus, the language of glycobiology makes use of components already present in the central dogma and its metabolic roots. This reflects a unity of biochemical networks and cellular function that suggests a deeper relationship.

Glycans and lectins represent new classes of molecules encoding and expressingbiological complexity. The structural diversity and functional

importance of glycans has led some researchers to propose that glycans represent the third language of biology. Cells communicate using glycans (on the cell surface or on secreted molecules) in a chemical language that has so far only been studied by experimental scientists (in a rather incomprehensive fashion). Currently, there is very little knowledge regarding the information content of this newly realized syntax. Because sugars can form both linear and branched 'words,' if one were to compare the glyco-code to an existing form of human language representation, we can perhaps consider depicting the language of glycans in Kanji or Hieroglyphic forms.

Workshop Topics and Organization:

The workshop will have five sessions devoted to the following topics:

Structural diversity of complex carbohydrates including biochemical pathways and evolution from prokaryotes to mammals:

Lectin-glycan interactions – Evolutionary, biochemical and biophysical studies: Data bases and mathematical/computational modeling:

Questions for theoretical glycobiology:

A sixth session will be devoted to future directions. A summary document will be prepared for publication.

Harold J. Morowitz

Professional Preparation

Yale University	Physics/Philosophy	B.S. (1947)
Yale University	Physics	M.S. (1950)
Yale University	Biophysics	Ph.D. (1951)

Appointments

1988 – present	Clarence Robinson Professor of Biology and Natural Philosophy, George Mason Univ
1993 – 1998	Director, Krasnow Institute for Advanced Study, George Mason University
1988	Visiting Scientist, Exobiology Section, NASA Ames Research Center
1974-80	Visiting Professor (Spring Quarter), University of California at Berkeley
1966-67	Visiting Professor of Microbiology, University of Hawaii
1955 – 1988	Yale University Assistant Professor, 1955-60; Associate Professor, 1960-67; Professor, 1967-88; Department of Molecular Biophysics & Biochemistry Director of Graduate Studies, 1963-64 Director of Undergraduate Studies 1964-74 Executive Committee 1968-77 Chairman – Health Professions Advisory Committee, 1975-77 Master, Pierson College 1981-86
1953 – 1955	Biophysicist, National Heart Institute, National Institutes of Health
1931 – 1953	Biophysicist, National Bureau of Standards

Publications

Five Publications Closely Related to the Current Project

1. Smith, E. and Morowitz, H.J., PNAS 101, 13168 (2004)
Universality in Intermediary Metabolism
2. Morowitz, H.J., Kostelnik, J.D., Yang, J., Cody, G.D. PNAS 97, 7704-7708, 2000
The Origin of Intermediary Metabolism
3. Cody, G.D., Boctor, N.Z., Hazen, R.M., Brandes, J.A., Morowitz, H.J., Yoder, H.S., Geochimica et
Cosmochimica Acta 65, 3557-3576, 2001
Geochemical Roots of Autotrophic Carbon Fixation
4. Morowitz, H.J., Complexity 4, 39-53, 1999
A Theory of Biochemical Organization, Metabolic Pathways and Evolution
5. Morowitz, H.J., Peterson, E., and Chang, S., Origin of Life and Evolution of the Biosphere 25, 295-
399, 1995
The Synthesis of Glutamic Acid in the Absence of Enzymes

Five Other Significant Publications:

1. Smith, T. and Morowitz, H.J., Journal of Molecular Evolution 18, 265, 1982
Between History and Physics
2. Nagle, J.F., Mille, M., and Morowitz, H.J., J. Chem. Phys. 72, 2959, 1980

4. Morowitz, H.J. PNAS 71, 2335, 1974
The Derivation of Ecological Relations from Physical and Chemical Principles
5. Bode, H., and Morowitz, H.J., J. Mol. Biol., 23, 191, 1967
Size and Structure of the Mycoplasma hominis H39 Chromosome

Synergistic Activities

Editorial Board of *Complexity* and *Biology and Philosophy*; author of *The Emergence of Everythin*
How the World Became Complex; Chairman, Science Advisory Board of the Santa Fe Institute. P
lic lectures presented at the National Defence University, Washington Academy of Sciences, AA
Indiana University, Harvard University.

Collaborations and Other Affiliations

Collaborators and co-editors (past 4 years): Shelley Copley, University of Colorado; D. Eric Smith, Santa Fe Institute; Vijayasarathy Srinivasan, George Mason University

Graduate and postdoctoral advisors:

Graduate Advisor: Ernest C. Pollard (deceased)

Graduate students supervised in the past five years: none

Postdoctoral research associates supervised in the past five years: none

David Eric Smith

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Professional Preparation

California Institute of Technology	Physics, Math	B.S., 1987
The University of Texas, Austin	Physics	Ph.D., 1993
The University of Texas, Austin	Postdoctoral Applied Research	1993 - 95

Appointments

2003	Research Professor, Santa Fe Institute
2000-03	Postdoctoral Fellow, Santa Fe Institute
1996-2000	Postdoctoral Fellow, Earth and Environmental Science Division Los Alamos National Laboratory
1996-2000	Research Scientist, Applied Research Laboratories The University of Texas, Austin
1993-95	Postdoctoral Fellow, Applied Research Laboratoreis The University of Texas, Austin

Publications

Five Publications Closely Related to the Current Project

Universality in intermediary metabolism, E. Smith and H. J. Morowitz, *Proc. Nat. Acad. Sci. USA*.**10**
13168 (2004)

Self-organization from structural refrigeration, E. Smith, *Phys. Rev.* E**68**, 046114 (2003)

Statistical mechanics of self-driven Carnot cycles, E. Smith, *Phys. Rev.* E**60,** 3633 (1999)

Carnot's theorem as Noether's theorem for thermoacoustic engines, E. Smith, *Phys. Rev.* E**58,** 2818
(1998)

Non-equilibrium phase transitions in a cellular signaling chain, S. Krishnamurthy, E. Smith, D
Krakauer, and W. Fontana, http://www.arxiv.org/list/q-bio/0312020, *Phys. Rev. Lett.*, (subm
ted)

Five Other Significant Publications

Quantitative model of price diffusion and market friction based on trading as a mechanistic random pr
ess, M. G. Daniels, J. D. Farmer, G. Iori, and E. Smith, *Phys. Rev. Lett.* **90**, 108102 (2003)

Statistical theory of the continuous double auction, E. Smith, J. D. Farmer, L. Gillemot, and S. Krishna
murthy, *Quantitative Finance* **3**, 481-514 (2003)

Evolving protein interaction networks through gene duplication, R. Pastor-Satorras, E. Smith, and R. V
Solé, J. *Theor. Biol.* **222**, 199-210 (2003)

Resonant scattering and localization in heterogeneous Biot media, E. Smith, *Phys. Rev. B*, **64,** 134202
(2001)

Universal slow dynamics in granular solids, J.A. TenCate, E. Smith, and R.A. Guyer, *Phys. Rev. Lett.*
1020 (2000)

Synergistic Activities

Innovations in teaching and training:
Wrote Draft Textbook on Modern Physics for Phys. 311 at U. T. Austin, 1990-1996. Chapters availab
in pdf from author.

Collaborations and Other Affiliations

Collaborators and co-editors (past 4 years): Nicholas P. Chotiros, Applied Research Laboratories; Sh
ley D. Copley, University of Colorado, Boulder; Marcus G. Daniels, Santa Fe Institute; J. Doyne Farm
Santa Fe Institute; Duncan K. Foley, New School University; Walter Fontana, Santa Fe Institute; Lasz
Gillemot, Santa Fe Institute; Robert A. Guyer, University of Massachusetts, Amherst; Giulia Iori, King
College London; Thomas B. Kepler, Duke University; David Krakauer, Santa Fe Institute; Supriya
Krishnamurthy, Trier University; Harold Morowitz, George Mason University; Romualdo Pastor-
Satorras, University of Catalunya; James N. Piper, Applied Research Laboratories; Martin Shubik,
Cowles Foundation, Yale University; Ricard V. Solé. Catalan Institute for Research and Advanced Stu
ies; James A. TenCate, Los Alamos National Laboratory.

Graduate and postdoctoral advisors:
Graduate Advisor:
Joseph G. Polchinski, University of California at Santa Barbara
Postgraduate Advisors:
Paul A. Johnson, Los Alamos National Laboratory
Nicholas P. Chotiros, Applied Research Laboratories, The University of Texas at Austin

Graduate students supervised in the past five years: none

Postdoctoral research associates supervised in the past five years: none

Total Students and Postdoctoral Researchers Supervised:
Graduate Students—0 Postdoctoral Researchers-- 0

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2. Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME

Joshi, Lokesh

POSITION TITLE

Associate Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(S)	FIELD OF STUDY
University of Bath, UK	Ph.D.	1994	Biochemistry
University of Rajasthan, Jaipur, India	M.S.	1989	Zoology
University of Rajasthan, Jaipur, India	B.S.	1987	Chemistry/Biology

A. Positions and Honors Positions and Employment

1994-1997	Postdoctoral Fellow, Molecular Biology, Boyce Thompson Institute at Cornell University, Ithaca NY
1997-2000	Research Associate Scientist, Glycobiology, Boyce Thompson Institute at Cornell University, Ithaca NY
2000-2003	Research Assistant Professor, School of Life Sciences and Department of Bioengineering, Arizona State University, Tempe, AZ
2003-Present	Associate Professor. Department of Bioengineering and The Biodesign Institute, Arizona State University, AZ
Jan 2004 June 2005	Acting Director - Center for Protein and Peptide Therapeutics, The Biodesign Institute, Arizona State University, AZ
July 2005 Present	Director - Center for Glycosciences and Technology, The Biodesign Institute, Arizona State University, AZ

Other Experiences and Professional Memberships

American Chemical Society; The Society of Glycobiology; American Society for the Advancement of Science, and American Society for Mass Spectrometric.

Honors

Annual Recognition Awards at Boyce Thompson Institute, Cornell University 1994-1998 Council of Vice Chancellors and Principals (CVCP) award. University of Bath, UK. 1991 British Council's Foreign and Commonwealth Office Award. 1990 Gold Medal, M.Sc. University of Rajasthan. 1989

B. Selected peer-reviewed publications (in chronological order).

Joshi L, St. Leger RJ, Roberts DW. 1997. Isolation of a cDNA encoding a novel subtilisin-like protease (Pr1B) from the entomopathogenic fungus, *Metarhizium anisopliae* using differential display-RT-PCR. *Gene*. 197, 1-8.

St. Leger RJ, **Joshi L.** 1997. Molecular methods for studying entomopathogenic fungi. In *"Practical guides to New Methods in Modern Biology -Manual of Techniques in Insect Pathology"* (Ed. L.A. Lacey). Academic Press. 367 394.

St. Leger RJ, **Joshi L,** Roberts DW. 1998. Ambient pH is a major determinant in the expression of

cuticle degrading enzymes and hydrophobin by *Metarhizium anisopliae*. *Applied and Environmental Microbiology*. 64 (2), 709-713.

St. Leger RJ, **Joshi L,** Roberts DW. 1998. Adaptation of proteases and carbohydrates of saprophytic, phytopathogenic and entomopathogenic fungi to the requirements of their ecological niches. *Microbiology*. 143, 1983-92

Joshi L, St. Leger RJ. 1999. Cloning, functional expression and substrate specificity of carboxypeptidase A secreted by the pathogenic fungus *Metarhizium anisopliae*. *Journal of Biological Chemistry*. 274 (14), 9803-9811.

Joshi L, Davis TR, Mattu TS, Rudd PM, Dwek RA, Shuler ML, Wood HA. 2000. The influence of baculovirus - host cell interaction on glycosylation of a recombinant protein. *Biotechnology Progress*. 16, 650-656.

Joshi L, Shuler MJ and Wood HA. 2001. Production of a sialylated N-linked glycoprotein in insect cells. *Biotechnology Progress*. 17, 822-827.

Kalidas C, **Joshi L**, Batt C. 2001. Characterization of glycosylated variants of beta-lactoglobulin expressed in *Pichia pastoris*. *Protein Engineering*. 14(3), 201-7.

Joshi L, Van Eck JM., Mayo K, Di Silvestro R., Blake (Nieto) ME, Ganapathi T, Haridas V, Gutterman JU, Arntzen CJ 2002. Metabolomics of plant saponins; Bioprospecting triterpene glycoside diversity with respect to mammalian cell targets. *OMICS: Journal of Integrative Biology*. 6(3), 235-245.

Shah MM, Fujiyama K, Flynn CR and **Joshi L.** 2003. Presence of sialylated endogenous glycoconjugates in plant cells. *Nature Biotechnology*. 21(12):1470-1471.

Tessier D, Komalavilas P, Panitch A, **Joshi L**, Brophy CM. 2003. The small heat shock protein (HSP) 20 is dynamically associated with the actin cross-linking protein actinin. *Journal of Surgical Research*. 111(1):152-7.

Flynn CR, Komalavilas, P, Tessier D, Thresher J, Niederkofler EE, Parmiter C, Nelson RW, Panitch A, **Joshi L**, Brophy CM. 2003. Transduction of Biologically-Active Motifs of the Small Heat Shock-related Protein, HSP20, Leads to Relaxation of Vascular Smooth Muscle. *FASEB Journal Express*. 17(10):1358-60. Epub 2003 May 08.

McLemore EC, Tessier DJ, Robert Flynn C, Furnish EJ, Komalavilas P, Thresher JS, **Joshi L,** Stone WM, Fowl RJ, Brophy CM. 2004. Transducible recombinant small heat shock-related protein, HSP20, inhibits vasospasm and platelet aggregation. Surgery.136(3):573-8.

Tessier DJ, Komalavilas P, Liu B, Kent CK, Thresher JS, Dreiza CM, Panitch A, **Joshi L,** Furnish E, Stone W, Fowl R, Brophy CM. 2004. Transduction of peptide analogs of the small heat shock-related protein HSP20 inhibits intimal hyperplasia. *Journal of Vascular Surgery*. 40(1):106-14.

Fletcher SP, Geyer BC, Smith A, Evron T, **Joshi L**, Soreq H, Mor TS. 2004. Tissue distribution of cholinesterases and anticholinesterases in native and transgenic tomato plants. Plant Mol Biol. 55(1):33-43.

McConnell EJ, McLemore EC, **Joshi L**, Nelson H. 2004. Depletion of activated Vbeta8++ T cells disrupts bispecific antibody directed antiumor immunity. *Journal of Surgical Research*. 122(1):103-12.

Dreiza CM, Brophy CM, Komalavilas P, Furnish EJ, **Joshi L,** Pallero MA, Murphy-Ullrich JE, von Rechenberg M, Ho YS, Richardson B, Xu N, Zhen Y, Peltier JM, Panitch A. 2005. Transducible heat shock protein 20 (HSP20) phosphopeptide alters cytoskeletal dynamics. FASEB J.19(2):261-3.

Lopes LB, Brophy CM, Furnish E, Flynn CR, Sparks O, Komalavilas P, **Joshi L**, Panitch A, Bentley MV. 2005. Comparative study of the skin penetration of protein transduction domains and a

conjugated peptide. *Pharm Res.* 22(5):750-7.

Flynn CR, Brophy CM, Furnish EJ, Komalavilas P, Tessier D, Thresher J, **Joshi L.** 2005. Transduction of phosphorylated heat shock-related protein 20, HSP20, prevents vasospasm of human umbilical artery smooth muscle. *J Appl Physiol.* 98(5):1836-45.

Joshi L, Lopez LC. 2005. Bioprospecting in plants for engineered proteins. *Current Opinion in Plant Biology.* 8:1-4.

Tran, N., Baral, C., Nagaraj, V.J. and **Joshi, L.** 2005. Knowledge-based framework for hypothesis formation in cellular biochemical networks. *Bioinformatics.* 21(Suppl 2):ii213-ii219.

Bogani F, McConnell E, **Joshi L**, Chang Y, Ghirlanda G. 2006. A Designed Glycoprotein Analogue of Gc-MAF Exhibits Native-like Phagocytic Activity. *J Am Chem Soc.* 128(22):7142-3.

Tangkuaram, T., J.Q. Gerlach, Y. Xiang, A.-N. Kawde, Z. Dai, V.P. Bhavanandan, J.T. La Belle, W. Veerasai, **L. Joshi***,
J. Wang*. 2006. Sensitive and Rapid Electrochemical Bioassay of Glycosidase Activity. *The Analyst.* 131: 889 891. * Corresponding authors

Z. Dai, A.-N. Kawde, Y. Xiang, J.T. La Belle, J.Q. Gerlach, V.P. Bhavanandan, **L. Joshi***, J. Wang*. 2006. Nanoparticle-Based Bioelectronic Sensing of Glycan-Lectin Interactions. *J Am Chem Soc.* 128: 10018-10019 . * Corresponding authors

Kilcoyne, M. **Joshi, L.** 2007. Carbohydrates in Cardiovascular and Hematological Therapeutics. Cardiovascular and Hematological Agents in Medicinal Chemistry. *In Press.*

C. Research Support

1. 0323421 L. Joshi (PI) 07/1/03-06/30/06 NSF "International collaboration on glycosylation studies of rabies virus glycoprotein produced in transgenic plants" The overall goal of this project is to produce correctly glycosylated oral vaccine against rabies.

1.2. L. Joshi (PI) 07/1/04-06/30/07 The Biodesign Institute, ASU "New initiatives in glycobiology - Human CHO project" We are introducing genes encoding different enzymes involved in complex mammalian-like glycosylation in plants.

2.3. L. Joshi (PI) 07/1/05-06/30/07 ASU School of Engineering Dean's Research Initiatives "Research Cluster in Integrated BioInspired Microsensors (IBIM) for Real-Time Detection of biomolecules" The goal of this interdisciplinary cluster is to develop novel label-free biosensors.

4. R01 HL070715 C. Brophy (PI) 04/01/03-03/31/07
NIH-NHLBI- "Prevention of vein graft spasm" The overall goal of this proposal is to study the biochemical and physiological events that help a small heat-shock-like protein HSP20 and its peptide form relax smooth muscles.

3.5. 05012164 C. Brophy (PI) 06/15/05-05/30/07 AzERx, LLC "Development of Vasoactive Therapeutic" This is the phase II or STTR grant developing a small peptide form of HSP20 into a therapeutic modality.

4.6. CK1205 L. Joshi (PI) 01/01/06-12/31/09 The Wallace Foundation "H.B. Wallace Research Initiative in the Center for Glycosciences & Technology" This Initiative is intended to explore glycosignatures on individual protein molecules and on cells.

5.7. Number pending L. Joshi (PI) 01/01/07-12/31/07 ASU-Mayo Collaborative Grants "Discovery and Validation of Novel Glycan-Binding Peptides specific for Cancer-Glycobiomarkers for the Detection of Pancreatic and Breast Cancers" A large library of synthetic peptides will be screened against the glycan population of cancer samples to identify and characterize peptide motifs that specifically bind to cancer-associated glycans.