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Original Paper

A Model for Enhancing the Science Workforce

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Abstract

This mini-review will focus on a US Presidential Award/National Science Foundation/ AAAS recognized program that offers research experiences for all interested students. The quality of the research experiences will be documented by citations of student (208 students) co-authored peer reviewed papers and evidence will be presented that students are turned on to research by the method of Oppenheimer mentoring, that will be described. The career outcomes of the students will be detailed and it will be shown that this program is a model for enhancing the science workforce.

1. Introduction

Many students want research experiences but can't get them, resulting in a science workforce deficit. Here 50 years of open door policy for research experiences will be described including quality of the research experiences, student co-authorships, student career outcomes and the effect of research experiences on students. The issue of professor ability to handle many new students is discussed. All students and trainers receive college credit and Steve Oppenheimer receives workload teaching credit for working with so many students.

2. Main Body

How can a single professor serve many new undergraduates in research?

Here's the answer edited from Oppenheimer, S., NATURE 519: 158 [90].

Handling so Many Undergraduates/Oppenheimer program

All new undergraduates are trained by peer undergraduates or pre-Masters students (not Ph.D. students or postdocs), experienced in the research, helping to insure that the newcomers immediately feel comfortable in the research setting. I, Steve Oppenheimer, regularly check all of the newcomers and liven it up with jokes and encouragement. The burden of heavy course loads is mitigated by an open

door policy that allows students to pursue their research during off hours and vacation times. This part of the program is very important for its success.

Hiring and Promotion. Edited from Oppenheimer, S., NATURE 554: 31 [91]

I suggest that skills in mentoring should be made a condition for hiring faculty members and that mentoring success be included as a criterion for tenure and promotion. This is done on our campus and may be a reason why our campus was listed as an up and coming research university by the NATURE INDEX. And that's with no Ph.D. students [94].

Obviously, many years of academic policy can't be changed overnight but the White House, NSF and AAAS think that our model is on the right track to change things for the better.

A specific example of student mentoring

Specific example of motivation putatively causing a specific career outcome.

An Hispanic Alum named Celina Barba Simic.

The documented career success of many hundreds of students mentored by Steve Oppenheimer played a key role in the U.S. Presidential Award as noted by the NSF Presidential Award peer review panel. The evidence presented is mostly correlation and does not provide any clarity on causal relationships. Serendipity has provided an example that gets more into possible causal relationships. This is about one student, of several, who made a donation to the university of student scholarship(s) in honor of Steve Oppenheimer. But in this case an astute reporter (93) unraveled how motivation by Steve Oppenheimer led to her acceptance to Stanford University Medical School (and is now a co-director of emergency medicine at a large Los Angeles Hospital). Here is some of her story in her own words. Her daughters asked, Mom, how did you become a doctor…In unraveling 20 years worth of layers she remembered Dr. Oppenheimer. She decided to make the gift to the university because she said Dr. Oppenheimer changed the trajectory of her life. It began when she took Oppenheimer's undergraduate embryology course. After that she worked in Oppenheimer's research lab. She said being in Dr. O's lab as an undergraduate was awesome. He encouraged every person that walked into the lab to do everything they wanted to do and helped them find ways to do it. She said Oppenheimer's encouragement made a profound impact on her life…He gave me the confidence to apply to medical school. He gave me the study skills, research skills and knowledge base to succeed. He said you're the best and you can become a doctor if you want to be one. He gave me the confidence to apply to medical school He changed the trajectory of my life. It's hard to assign causality to motivational strategies. But this story comes close.

Boundless enthusiasm

One item that caught the eye of a NSF panel reviewer on the Presidential Award panel: He (Oppenheimer) calls his students professors and doctors. I'm going to try doing that. It's a motivational gimmick that is both inspirational and transformative that reflects his boundless enthusiasm (89).

I will now summarize some of the research done by undergraduates and pre-Masters students over a 50 year period, listing number of student co-authors on each component of this program. Numbers refer to

citation on the reference list. If no students are listed next to a citation, no students co-authored it. These listings help document the quality of student co-authored peer-reviewed papers in this program.

3. Sea Urchin Embryo

We examined the molecular basis of adhesive interactions in the sea urchin embryo, an NIH model system. 5 (1 student), 6 (3 students), 9 (3 students), 10 (3 students), 11, 12 (2 students), 16 (1 student), 19 (3 students), 20 (1 student), 21 (2 students), 22 (2 students), 25 (2 students), 28, 29, 30, 31 (2 students), 32 (3 students), 35 (1 student), 38 (6 students), 40, 42 (4 students), 43 (7 students), 44 (3 students), 49 (2 students), 50, 51 (5 students), 53 (4 students), 54 (13 students), 55 (7 students), 56 (1 student). 57 (5 students), 58 (3 students), 67, 69, 73 (1 student), 75, 79 (3 students), 81 (2 students), 83 (1 student), 84 (3 students), 85, 86, 87 (1 student). As can be seen (5, 9, 10, 12, 20, 21, 22, 25, 32, 35, 66, 67, 69, 70, 71, 76, 77, 78, 79, 80, 81, 83, 84, 85, 87) were in NATURE, SCIENCE, ZYGOTE, EXPERIMENTAL CELL RESEARCH, CRYOBIOLOGY, BIOCHEMICA BIOPHYSICA ACTA, journals that are known for high quality papers and usually good impact factors. The student co-authored research helped show that specific carbohydrates were involved in sea urchin embryo cellular interactions, a finding that helped lead to election as Fellow AAAS and a US Presidential Award for mentoring.

4. Cancer and Assays

The area of cancer is exciting for students and we made discoveries on cancer clumps vs single cells, cancer cell adhesiveness, cancer cell protease and cancer cell surfaces. 7 (2 students), 8 (1 student), 13 (2 students), 14, 15 (1 student), 17 (2 students), 18 (7 students), 23 (17 students), 24 (13 students), 26 (1 student), 33 (2 students), 34 (1 student), 36 (1 student), 39 (3 students), 41 (2 students), 45 (18 students), 47 (10 students), 52 (3 students), 59 (3 students) 60, 61, 62, 63, 64, 65, 66 (4 students), 68, 70 (3 students), 71 (4 students), 72 (3 students), 74, m75, 76 (3 students), 77 (1 student), 78, 82, 87 (1 student), 88, 89. 46 (7 students), 48.

5. Who Writes the Student Co-Authored Papers?

I do for some of them. The students and I do most of them. The students do for others. Our biggest paper with 10,000 downloads was totally student written (7). The writer, Haike Ghazarian, is now a Ph.D. working in industry. I am reprinting this paper below as it is for non-profit education purposes and it is a masterpiece. This paper is an example of the high level of student co-authorships that reflects their training and why this program is a model for enhancing the science workforce.

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Review

A glycobiology review: Carbohydrates, lectins and implications in cancer therapeutics

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ABSTRACT

This review is intended for general readers who would like a basic foundation in carbohydrate structure and function, lectin biology, and the implications of glycobiology in human health and disease, particularly in cancer therapeutics. These topics are among the hundreds included in the field of glycobiology and are treated here because they form the cornerstone of glycobiology or the focus of many advances in this rapidly expanding field.

Contents

Abbreviations: APC, antigen presenting cell; B4GALNT2, β-1,4-N-acetyl-galactosaminyltransferase; CDKL5, cyclin-dependent kinase-like 5; CNS, central nervous system; Con A, concanavalin A; CRD, carbohydrate recognition domain; CTL, C-type lectin; C2GnT, β-1,6-N-acetylglucosaminyltransferase; DDS, drug delivery system; Dnmt1, DNA methyltransferase 1; ECM, extracellular matrix; EGF, epidermal growth factor; ER, endoplasmic reticulum; GlcNAc-TV, β-1,6-N-acetylglucosaminyltransferase V; GlcNAc-TIII, β-1,4-N-acetylglucosaminyltransferase III; HCC, hepatocellular carcinoma; HEV, high endothelial venule; HIV, human immunodefiency virus; KLH, keyhole limpet hemocyanin; LacNAc, N-acetyllactosamine; MASP, MBP associated serine proteases; MBP, mannose-binding protein; MGAT5, mannoside-acetylglucosaminyltransferase 5; MHC, major histocompatibility complex; ML-I, mistletoe lectin I; MR, mannose receptor; NLS, nuclear localizing signal; O-GlcNAc, O-linked β-N-acetylglucosamine; PHA-I, *Phaseolus vulgaris agglutinin*; SCR, short consensus repeat; SOS, sialyloligosaccharides; TCR, T cell receptor; VEGF, vascular endothelial growth factor; α-1, 6-FT, α-1,6-fucosyltransferase; 5-aza-dC, 5-aza-2′-deoxycytidine; sLe^a, sialyl Lewis^a; sLe^x, sialyl Lewis^x

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Introduction

For over a century, the areas of nucleic acids, proteins and lipids have captured the attention of investigators worldwide. Carbohydrates, probably because they are very complex and not encoded in the genome, have only more recently received increased attention through the expanding field of glycobiology. The aim of this review is to provide general readers with an instructionally useful discussion of three fundamental areas in the field of glycobiology: (1) carbohydrate structure and function; (2) lectins; (3) roles for glycobiology in human health and disease, particularly in cancer therapeutics. The first area was chosen to improve the understanding of general readers regarding the nature of carbohydrate structure and function, the framework upon which glycobiology is based. The second was selected because lectins are perhaps the most widely studied molecules in glycobiology. The last topic was included because of the many exciting advances being made in glycobiological aspects of disease therapeutics. This review will provide a discussion of these topics and will provide a useful teaching tool to introduce students and investigators to this exciting field.

Carbohydrate structure

The four major classes of organic molecules in living systems are proteins, lipids, nucleic acids and carbohydrates. Carbohydrates are by far the most abundant organic molecules found in nature, and nearly all organisms synthesize and metabolize carbohydrates (Wade, 1999). The term carbohydrate arose from the fact that most simple sugars have the empirical formula $C_nH_{2n}O_n$, where n is ≥ 3, suggesting that carbon atoms are in some way combined with water. Chemists referred to these compounds as "hydrates of carbon" or "carbohydrates" (Wade, 1999). Glucose, for example, is a common monosaccharide that is oxidized to form carbon dioxide and water, providing energy for cellular processes such as protein synthesis, movement and transport. Plants and animals link numerous glucose molecules together to form large energy-storing molecules such as starch and glycogen. However, glucose molecules may be linked to form a variety of other macromolecules. Cellulose is a component of the cell wall in plants and it is composed of glucose molecules linked together through β-1,4 glycosidic bonds. The glucose monomers in starch, on the other hand, are linked through α-1,4 glycosidic bonds, and the glycosidic bonds of glycogen are α-1,4 and α-1,6 (Wade, 1999).

The complex heterogeneity of carbohydrates in living systems (Fig. 1) is a direct result of several carbohydrate characteristics: the ability of different types and numbers of sugar residues to form glycosidic bonds with one another, the structural characteristics of these molecules, the type of anomeric linkage, the position and the absence or presence of branching (Mody et al., 1995; Gorelik et al., 2001). To illustrate the exponential increase in the complexity of a single disaccharide molecule composed of two identical molecules of a single hexose monosaccharide, glucose for example, one may compare it with a single dipeptide composed of two identical molecules of a single amino acid such as glycine. The former can produce 11 different disaccharides, but the latter can only produce a single dipeptide. On a larger scale, four different amino acids may form 24 different tetrapeptides, but four different hexose monosaccharides may potentially produce 35,560 unique tetrasaccharides (Sharon and Lis, 1989, 1993). What is intriguing about the ability of glycans to encode an immense repertoire of biological information is that they are not encoded by the genome (Feizi and Mulloy, 2003). The genome codes for enzymes that act on glycans such as glycosyltransferases and glycosidases. The combined activity levels of these enzymes in the endoplasmic reticulum (ER) and the Golgi apparatus, and perhaps on the cell surface, determine the glycosylation patterns (carbohydrate domains) of glycolipids

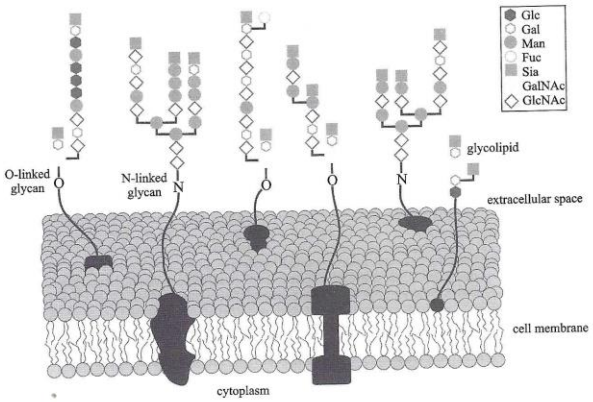

Fig. 1. Schematic illustration of carbohydrate heterogeneity found on cell surface glycoproteins and glycolipids. Sialic acids (Sia) are usually found at the terminal residue of O-linked and N-linked glycans of glycoproteins and glycolipids. Glc, glucose; Gal, galactose; Man, mannose; Fuc, fucose; GalNAc, N-acetylgalactosamine; GlcNAc, N-acetylglucosamine. Illustration prepared by Haike Ghazarian using Corel Draw X4.

and glycoproteins (Sharon, 1980; Opdenakker et al., 1993; Zheng et al., 1993). For a more complete and in-depth discussion of carbohydrate structure, chemistry, synthesis and function we highly recommend reviewing Chapter 23 of the Wade *Organic Chemistry* (Wade, 1999) textbook and *Introduction to Glycobiology* (Taylor and Drickamer, 2006).

Carbohydrate function

The structural variability and complexity of cell surface glycans allows them to function as signaling molecules, recognition molecules and adhesion molecules (Sharon and Lis, 1989, 1993; Ofek et al., 2003a,b). As such, cell surface glycans are involved in many physiologically important functions that include normal embryonic development, differentiation, growth, contact inhibition, cell–cell recognition, cell signaling, host–pathogen interaction during infection, host immune response, disease development, metastasis, intracellular trafficking and localization, rate of degradation and membrane rigidity (Sharon, 1980; Akiyama et al. ,1989; Sharon and Lis, 1989, 2003; Chammas et al., 1991; Opdenakker et al., 1993; Zheng et al., 1993; Mody et al., 1995; Disney and Seeberger, 2004; Nimrichter et al., 2004; Zachara and Hart, 2006; Blomme et al., 2009; Mukhopadhyay et al., 2009). Although the physical and chemical properties of simple carbohydrates are well known, it is unfortunate that we cannot say the same for complex carbohydrates in living systems. Glycobiology is a fertile area that we are just beginning to understand and appreciate. Studies in glycobiology have been advancing at ever increasing rates in the past few years driven by advanced developments in new technologies and in genomics (Wormald and Sharon, 2004; Oppenheimer et al., 2008; Goetz et al., 2009; Powlesland et al., 2009; Rek et al., 2009; Struwe et al., 2009; Yamanaka et al., 2009; Zhang et al., 2009).

Glycosylation pattern alterations in cancer development

Normal cells have to overcome multiple levels of regulation in order to transform into metastatic malignant cells that eventually invade neighboring or distant tissues. Genetic alterations allow malignant cells to over-express growth signals and become indifferent to the inhibitory effects of tumor suppressor gene products such as Rb and p53. Certain genetic changes further allow the reactivation of telomerase activity creating an extensive replication potential (Couldrey and Green, 2000). In addition to genetic alterations, phenotypic alterations also provide malignant cells the ability to escape tissue boundaries through engulfment, invasion and angiogenesis. Other phenotypic changes provide malignant cells with mechanisms to escape immunosurveillance (Couldrey and Green, 2000; Schwartz-Albiez et al., 2008).

The phenotypic alterations of interest here are those of the cell surface carbohydrates. Nearly all types of malignant cells and cells of many types of diseased tissues demonstrate alterations in their glycosylation patterns when compared to their normal counterparts (Hakomori, 1985, 1989, 1996; Dennis, 1992; Mody et al., 1995; Fukuda, 1996; Orntoft and Vestergaard, 1999; Oppenheimer, 2006; Blomme et al., 2009; Danussi et al., 2009; Patsos et al., 2009; Pettersson-Kastberg et al., in press; Powlesland et al., 2009; Shida et al., 2009). The alterations in glycosylation patterns are often a result of altered activities of glycosyltransferases and glycosidases as is evident in the specific and preferential display of certain glycoconjugates on cancer cells (Mody et al., 1995; Couldrey and Green, 2000; Gorelik et al., 2001; Oppenheimer, 2006; Schwartz-Albiez et al., 2008; Blomme et al., 2009; Goetz et al., 2009; Patsos et al., 2009; Powlesland et al., 2009; Rek et al., 2009; Shida et al., 2009).

N-linked and O-linked oligosaccharides

Oligosaccharides can form glycosidic bonds with proteins by two types of linkages. The first type involves the binding of N-acetylglucosamine to the amide side chain of asparagine (N-linked). Asparagine residues with N-linked carbohydrates are of the sequence Asn-X-Ser(Thr)-, where X can be any amino acid except proline (Gorelik et al., 2001). The second type involves the binding of C-1 of N-acetylgalactosamine to the hydroxyl of serine or threonine (O-linked) (Gorelik et al., 2001). A full description of N- and O-linked glycosylation and their biological significance is beyond the scope of this brief review. We will provide a few examples with brief descriptions of their biological significance. We encourage reading *Introduction to Glycobiology* (Taylor and Drickamer, 2006) for a more in-depth exploration of these topics.

N-linked glycosylation in eukaryotes is initiated by the covalent addition of a 14 carbohydrate-long common oligosaccharide precursor (2N-acetylglucosamine, 9 mannose and 3 glucose) to the asparagine of the target polypeptide chain (core protein) as the newly synthesized polypeptide chain is translocated into the ER. This 14 carbohydrate common precursor gives rise to three major classes of N-linked oligosaccharides: (1) high-mannose oligosaccharides, (2) complex oligosaccharides and (3) hybrid oligosaccharides. N-linked glycosylation is required for the proper folding of some eukaryotic proteins in the ER. Three glucose residues are removed from the precursor N-linked oligosaccharide of the correctly folded protein and the glycoprotein is then exported from the ER to the Golgi apparatus. In the Golgi apparatus, mannose residues may be removed and other monosaccharides (e.g. N-acetylglucosamine, N-acetylgalactosamine, galactose, fucose and sialic acid) may be added in their place to elongate the N-linked oligosaccharides. These carbohydrate residue modifications in the Golgi apparatus provide the means by which complex and hybrid N-linked oligosaccharides are synthesized. Furthermore, different portions of the protein may potentially be glycosylated by all three major classes of N-linked oligosaccharides.

O-linked glycosylation is a modification of glycoproteins that is most likely catalyzed in the Golgi apparatus (Rottger et al., 1998). Here, the C-1 of N-acetylgalactosamine is covalently bonded to the hydroxyl of serine or threonine of the target polypeptide chain (core protein) (Rottger et al., 1998; Patsos et al., 2009). Once the N-acetylgalactosamine residue has been added, the elongation of the O-linked oligosaccharides may then proceed by the addition of other carbohydrate residues such as galactose, fucose, N-acetylglucosamine and sialic acid (Schachter and Brockhausen, 1992; Mitra et al., 2006). Several different types of O-linked oligosaccharides have been identified (e.g. O-fucose, O-mannose, O-glucose and O-N-acetylglucosamine). The dynamic modification of proteins with O-linked β-N-acetylglucosamine (O-GlcNAc) has been shown to play a role in modulating protein activity via different mechanisms: (1) modifying protein function through phosphorylation, (2) regulating protein–protein interactions, (3) regulating protein degradation, (4) protein localization and (5) regulating transcription (Hanover, 2001; Zachara and Hart, 2006; Hart et al., 2007). In many site-mapping studies, the sites of attachment for O-phosphate and O-GlcNAc were mapped to the same residue (Zachara and Hart, 2006; Hart et al., 2007). These data suggest that O-phosphate and O-GlcNAc modify proteins by competing for the same serine or threonine residues. Therefore, by modifying the available serine or threonine residues

available for phosphorylation, O-GlcNAc regulates protein function by varying phosphorylation patterns (Zachara and Hart, 2006).

Carbohydrate–protein interactions

Protein degradation is also vital in regulating cellular processes and survival. Proteins such as cell cycle regulators, anti-apoptotic proteins, transcription factors and tumor suppressors must be degraded in a timely fashion to maintain homeostasis. Furthermore, it has been shown that proteins modified with O-GlcNAc are efficiently shuttled from the cytoplasm to the nucleus in *Aplysia* neurons, suggesting that O-GlcNAc may function as either an alternative nuclear localizing signal (NLS) or as a nuclear retention signal (Zachara and Hart, 2006; Hart et al., 2007). In addition, the transcription of numerous genes is either up- or down-regulated by transcription factors that are O-GlcNAc modified (Hanover, 2001; Zachara and Hart, 2006). The above example and the five mechanisms of protein modification demonstrate the ability of glycosylation to alter cellular activity at many levels. Therefore, alteration in glycosylation may eventually lead to chronic diseases such as cancer or may be a result, not a cause, of associated changes (Blomme et al., 2009; Danussi et al., 2009; Patsos et al., 2009; Pettersson-Kastberg et al., in press; Powlesland et al., 2009; Shida et al., 2009). Covalent modification of proteins and enzymes through phosphorylation and dephosphorylation is a sophisticated control system that cells utilize to maintain homeostasis (Voet et al., 1999). Thus, entire or possibly multiple enzyme cascade pathways and signaling pathways are influenced. This in turn, as described above, may affect the activation or the inhibition of transcription factors, cell cycle regulators, apoptotic proteins and tumor suppressors.

Studies suggest that activated kinases, via phosphorylation or dephosphorylation, interact with DNA methyltransferases thus activating or deactivating them. DNA methyltransferase 1 (Dnmt1) is an enzyme that recognizes and methylates hemi-methylated CpG after DNA replication to maintain methylation patterns. Researchers found that an active 110-kDa protein kinase, identified as cyclin-dependent kinase-like 5 (CDKL5), phosphorylated the N-terminal region of Dnmt1 in the presence of DNA (Kameshita et al., 2008). The Sd^a blood group carbohydrate structure (GalNAc-β-1,4-[NeuAc-α-2,3]-Gal-β-1,4-GlcNAc-R) display is significantly reduced in malignant gastrointestinal cells but it is displayed abundantly in their normal counterparts. Treatment of malignant gastrointestinal cells with 5-aza-2′-deoxycytidine (5-aza-dC), an inhibitor of DNA methyltransferase, resulted in the display of Sd^a at the cell surface and the transcription of β-1,4-N-acetyl-galactosaminyltransferase (B4GALNT2), which catalyzes the synthesis of Sd^a. It was also found that the promoter region of the human B4GALNT2 gene was extensively hypermethylated in many malignant gastrointestinal cell lines studied as well as in gastric cancer tissue. It is evident that DNA hypermethylation contributed to the down-regulation of the B4GALNT2 gene, thus, silencing the activity of these enzymes, which eventually led to the aberrant glycosylation and display of cancer-associated carbohydrate antigens (Karp, 2002; Kawamura et al., 2008). It was described earlier that O-phosphate and O-GlcNAc compete for the same serine or threonine residues therefore altering the serine or threonine residues available for phosphorylation. This altered phosphorylation pattern then changes enzyme cascade and signaling pathways, which consequently influence expression levels of genes that encode, for example, glycosyltransferases and glycosidases. The altered activity levels of glycosyltransferases and glycosidases account for the specific and preferential display of certain glycoconjugates on cancer cells (Mody et al., 1995; Couldrey and Green, 2000; Gorelik et al., 2001; Oppenheimer, 2006; Schwartz-Albiez et al., 2008; Blomme et al., 2009; Danussi et al., 2009; Patsos et al., 2009; Pettersson-Kastberg et al., in press; Powlesland et al., 2009; Shida et al., 2009). In hepatocellular carcinoma (HCC), for example, the activities of α-1,6-fucosyltransferase (α-1,6-FT), β-1,6-N-acetylglucosaminyltransferase V (GlcNAc-TV) and β-1,4-N-acetylglucosaminyltransferase III (GlcNAc-TIII) are significantly increased compared to their normal counterparts (Blomme et al., 2009). In addition, GlcNAc-TIII activity in HCC is much higher than that of GlcNAc-TV during the precancerous stages of hepatocarcinogenesis. GlcNAc-TV activity, however, is more prominent in the more advanced stages of HCC compared to the precancerous stages (Blomme et al., 2009).

Cancer cell glycans

Experimental evidence collected for several decades on various cancer cell systems has revealed that malignant transformation is associated with a variety of altered cell glycosylation patterns. These aberrations in carbohydrate patterns are observed in glycolipids, glycosphingolipids and glycoproteins (Hakomori, 1985, 1989, 1996; Dennis, 1992; Fukuda, 1996; Danussi et al., 2009; Goetz et al., 2009; Patsos et al., 2009; Powlesland et al., 2009; Rek et al., 2009; Shida et al., 2009). Glycolipid carbohydrate alterations have been more accurately described since specific glycolipids can be isolated and structurally defined (Shida et al., 2009), whereas the carbohydrates of glycoproteins are usually heterogeneous (Hakomori, 1985). Glycosylation changes in malignant cell glycolipids are based on two mechanisms: (1) neosynthesis or (2) inhibition of carbohydrate synthesis. Sialic acid containing glycosphingolipids (gangliosides) are displayed mainly in the plasma membrane where they are involved in cell growth and differentiation (Gorelik et al., 2001; Shida et al., 2009). The sialic acids are a family of carbohydrates that have a nine carbon backbone in common, and they are typically found at the terminal position of several classes of secreted and cell surface glycan molecules (Varki, 2007). Gangliosides such as GD3 are abundantly displayed in tumors of epithelial or neuroectodermal origin: teratomas, head cancers, breast cancer, neck tumors, neuroblastoma, glioma, melanoma and medulloblastoma (Hakomori, 1985; Manfredi et al., 1999; Zeng et al., 1999, 2000). *In vitro* studies demonstrated a mechanism by which ganglioside accumulation may promote tumor growth. It was shown that exogenous GD3 gangliosides stimulated vascular endothelial growth factor (VEGF) production by tumor cells (Koochekpour et al., 1996), while rat F-11 tumor cells transfected with antisense GD3-synthase cDNA showed reduced GD3 display and reduced tumor growth (Zeng et al., 1999). It was found that the ability of GD3 gangliosides in stimulating neoangiogenesis was dependent on the ratio of GM3:GD3. Stimulation of angiogenesis was induced by a decrease in the ratio of GM3:GD3 while inhibition of angiogenesis was induced by an increase in the ratio of GM3:GD3 (Ziche et al., 1992).

Meticulous studies of cell surface carbohydrates from human and experimental tumors showed that a prominent alteration in glycoproteins is the presence of larger and extensively branched N-linked β-1,6-GlcNAc oligosaccharides (Dennis, 1991, 1992; Fernandes et al., 1991; Mody et al., 1995; Orntoft and Vestergaard, 1999; Couldrey and Green, 2000). The β-1,6-GlcNAc branched N-glycans are tri- or tetra-antenna oligosaccharides that increase the total cell surface terminal sialylation in malignant cells, and are typically found in the initial stages of carcinogenesis induced by oncogenic viruses or by oncogenes (Yamashita et al., 1985; Pierce and Arango, 1986; Dennis et al., 1987, 1989). It is thought

that the increased levels of α-1,2 sialylation in the Golgi apparatus may be responsible for the metastatic potentials of malignant cells (Dennis et al., 1986). The increased β-1,6 branching of N-linked oligosaccharides is due to increased activity of GlcNAc-TV, also known as MGAT5 (mannoside-acetylglucosaminyltransferase 5). This increased activity is in part due to increased expression of the (GlcNAc-TV) gene, which is correlated with malignant transformation (Orntoft and Vestergaard, 1999; Couldrey and Green, 2000; Gorelik et al., 2001). Many other carbohydrate structures such as sialyl Lewis^a (sLe^a) (NeuAc-α-2,3-Gal-β-1, 3-[Fuc-α-1,4]-GlcNAc) and sialyl Lewis^x (sLe^x) (NeuAc-α-2,3-Gal-β-1,4-[Fuc-α-1,3-]-GlcNAc), including other sialyl Lewis isomers present on O- and N-linked oligosaccharides, have been shown to be displayed in various human malignancies (Gorelik et al., 2001; Sharon and Lis, 2004; Danussi et al., 2009; Goetz et al., 2009; Patsos et al., 2009; Powlesland et al., 2009; Rek et al., 2009; Shida et al., 2009;). Immunohistochemical staining studies have demonstrated that sLe^a and sLe^x, whose synthesis depends on the activity of β-1,6-N-acetylglucosaminyltransferase (C2GnT), are not displayed in normal breast epithelial cells, but are found in primary breast carcinoma (Renkonen et al., 1997). Display of these structures is associated with advanced forms of malignancies and poor prognosis in breast, bladder, lung and colon carcinomas (Miyake et al., 1992; Irimura et al., 1993; Nakamori et al., 1993; Shimodaira et al., 1997; Orntoft and Vestergaard, 1999). Interestingly, in a study of 46 colorectal cancer patients, 63% of cancer tissues studied expressed C2GnT, while no expression of C2GnT was seen in normal mucosa of all 46 patients. Furthermore, C2GnT mRNA was detected in 68% of malignant cells with sLe^a as compared to 58% of malignant cells having sLe^x (Shimodaira et al., 1997). It has been suggested that malignant cell glycosylation patterns and tumor progression towards more malignant phenotypes is not coincidental (Gorelik et al., 2001). However, it is worth noting that observed alterations in malignant cell surface oligosaccharides do not prove, but suggest, the involvement of carbohydrates in the metastatic potentials of malignant cells because the mechanisms through which glycans are associated with metastasis remain unclear (Gorelik et al., 2001; Danussi et al., 2009; Patsos et al., 2009; Powlesland et al., 2009; Rek et al., 2009; Shida et al., 2009).

Lectins

It is difficult to discuss carbohydrates without reference to lectins. Lectins are defined as proteins that preferentially recognize and bind carbohydrate complexes protruding from glycolipids and glycoproteins (Mody et al., 1995; Gorelik et al., 2001; Bies et al., 2004; Minko, 2004). The term lectin is derived from the Latin word *legere* meaning "to choose" or "select", and has been generalized to encompass all non-immune carbohydrate-specific agglutinins regardless of blood-type specificity or source (Sharon and Lis, 2004). The interaction of lectins with particular carbohydrates can be as specific as the interaction between those of antigen and antibody or substrate and enzyme (Minko, 2004). Lectins bind not only to oligosaccharides on cells but also to free-floating glycans including monosaccharides. Lectin–monosaccharide interactions, however, are relatively weak with dissociation constants often on the order of micromolar to millimolar range (Bouckaert et al., 2005; Rabinovich et al., 2007).

The beginnings of lectinology date back to 1888 when Herrmann Stillmark described the agglutination properties of ricin; however, the modern age of lectinology started nearly 100 years later (Bies et al., 2004; Sharon and Lis, 2004). Lectins were initially found and described in plants, but in subsequent years multiple lectins were isolated from microorganisms and also from animals (Sharon and Lis, 2004). Interestingly plant and animal lectins show no primary structural homology, yet they demonstrate similar preferential binding to carbohydrates. This suggests that animal and plant lectin genes may have co-evolved, thus highlighting the importance of lectin–carbohydrate interactions in living systems (Gorelik et al., 2001). During the past several years, however, many primary and three-dimensional structures of lectins have been elucidated. It was observed that lectins from diverse sources lacked primary sequence similarity but shared similarities in their tertiary structures (Sharon and Lis, 2004). Structural studies conducted on animal lectins suggested that the carbohydrate-binding activity of most lectins was generated by limited amino acid residues designated as the carbohydrate recognition domain (CRD) (Sharon and Lis, 2004). The CRD typically recognizes the terminal non-reducing carbohydrate residues of cell membrane glycoproteins and glycolipids (Mody et al., 1995). Lectin CRDs also may discriminate between anomeric isomers as a function of their specificities. For example, the lectin concanavalin A (Con A) specifically binds the α-anomer of glucose and mannose, but not the β-anomer of either (Mody et al., 1995).

Lectin families

Within the animal lectins, several highly conserved CRD amino acid sequences have been identified, thus allowing investigators to categorize the majority of these lectins into structurally related families and superfamilies (Sharon and Lis, 2004). C-type lectins (CTLs) are the most abundant of all animal lectins, and the CTL superfamily is grouped into three families: selectins, collectins and endocytic lectins (Sharon and Lis, 2004; Kerrigan and Brown, 2009). A majority of CTLs are large, asymmetric, have one or more CRDs and exist as Ca^{2+}-dependent proteins found in secreted or bound forms (Gorelik et al., 2001; Sharon and Lis, 2004). In contrast, the S-type lectins (galectins) in the CTL superfamily are generally small, non-glycosylated, soluble and exist as Ca^{2+}-independent proteins found intracellularly and extracellularly (Drickamer and Taylor, 1993; Barondes et al., 1994; Drickamer, 1995; Cooper and Barondes, 1999; Minko, 2004; Sharon and Lis, 2004; Chou et al., 2009; Malik et al., in press; Saravanan et al., in press). Currently at least 10 galectins have been identified and all bind N-acetyllactosamine (Gal-β-1-nGlcNAc-R) by recognizing the β-gal residue (Gorelik et al., 2001). The collectin family of CTLs includes collagenous lectins such as mannose-binding proteins (MBPs), pulmonary surfactant SP-A and SP-D and conglutinin (Gorelik et al., 2001; Kerrigan and Brown, 2009; Ruseva et al., 2009). The selectin family of CTLs includes the E-, L- and P-selectins. These selectins have a single epidermal growth (EGF)-like domain, an extracellular CRD, a cytoplasmic tail, a transmembrane domain, and two to nine short consensus repeat (SCR) units that are homologous to complement binding proteins (Stoolman, 1989; Varki, 1994; Tedder et al., 1995; Sharon and Lis, 2004). Selectins specifically bind oligosaccharides such as sLe^a and sLe^x or their sulfated equivalents (Varki, 1994; Sharon and Lis, 2004). Another lectin family of special interest is the siglecs. The siglecs are sialic acid-binding Ig-like lectins and belong to the Ig superfamily. They carry unique expression patterns in different cells, indicating that they are involved in highly specialized and specific cellular processes (Sharon and Lis, 2004; Yamanaka et al., 2009).

Biological significance of lectins

Endogenous lectins are involved in an enormous variety of biological processes as indicated by an increasing volume of data concerning them (Mody et al., 1995; Gorelik et al., 2001;

Minko, 2004; Nimrichter et al., 2004; Sharon and Lis, 2004; Wormald and Sharon, 2004; Rabinovich et al., 2007; Kerrigan and Brown, 2009). A complete and in-depth discussion of the biological significance of lectins is not within the scope of this brief review, however, a discussion of a few mammalian system examples is warranted. Endogenous lectins mediate biological processes such as cell–cell self-recognition, cell–extracellular matrix (ECM) interactions, gamete fertilization, embryonic development, cell growth, cell differentiation, cell signaling, cell adhesion and migration, apoptosis, immunomodulation and inflammation, host–pathogen interactions, glycoprotein folding and routing, mitogenic induction and homeostasis (Mody et al., 1995; Gorelik et al., 2001; Minko, 2004; Nimrichter et al., 2004; Sharon and Lis, 2004; Wormald and Sharon, 2004; Rabinovich et al., 2007; Chou et al., 2009; Kerrigan and Brown, 2009; Malik et al., in press; Ruseva et al., 2009; Saravanan et al., in press; Yamanaka et al., 2009).

Selectin functions

In the immune system, endogenous lectins are an important component of the host's defense against invading pathogens (Weis et al., 1998; Sharon and Lis, 2004; Wormald and Sharon, 2004; Rabinovich et al., 2007; Kerrigan and Brown, 2009; Malik et al., in press). In the innate immune system lectins are able to directly kill microorganisms, or they may aid in the phagocytosis of invading pathogens by dendritic cells and macrophages (Weis et al., 1998; Sharon and Lis, 2004; Kerrigan and Brown, 2009). The phagocytosed pathogens are neutralized and their proteins are processed into small peptides that are presented to T lymphocytes as a peptide-major histocompatibility complex (MHC). This antigen presentation activates specific immune responses and, therefore, lectins are also involved in the adaptive immune system (Gorelik et al., 2001). This is an example of indirect lectin involvement in the adaptive immune system. Lectins, however, are also directly involved in adaptive immunity. Leukocytes express L-selectins, members of the CTL superfamily, and these L-selectins aid in the homing capabilities of leukocytes (Tedder et al., 1995). Interestingly, naïve T lymphocyte expression of L-selectins is high but, once activated, the L-selectin expression is low or lacking altogether. The elevated levels of L-selectin expression by naïve T lymphocytes allow them to migrate to the lymph nodes by binding to specialized high endothelial venules (HEV), where they mature and become activated when presented with the proper antigens. In the latter case, the lack of L-selectin expression by activated T lymphocytes allows them to migrate and exit at the site of inflammation via high affinity interaction between integrins and their specific ligands (Gorelik et al., 2001). This L-selectin expression level-dependent behavior of T lymphocytes has been demonstrated in studies in which T lymphocytes from tumor-bearing mice were restimulated *in vitro* and selected for their L-selectin expression levels. It was found that T lymphocytes with low L-selectin expression levels efficiently eradicated brain and pulmonary tumors while T lymphocytes with elevated levels of L-selectins demonstrated noticeably reduced tumor clearance abilities (Kagamu and Shu, 1998; Kjaergaard and Shu, 1999).

Collectin functions

Collectins, also members of the CTL superfamily, are thought to be involved in the pattern recognition of respiratory viruses and pathogenic bacteria (White et al., 2000). MBP is an example of a protective collectin (Ikeda et al., 1987; Kuhlman et al., 1989; Schweinle et al., 1989; Stahl and Ezekowitz, 1998) that is able to bind oligomannose residues of bacterial and fungal cell surface oligosaccharides. The structural homology between the C1q component of the complement system and the collagen-like domain of MBP allows for the initiation of complement fixation upon MBP–pathogen binding (Gorelik et al., 2001). The initiation of complement fixation is brought about by the activation of MBP associated serine proteases (MASP-1 and MASP-2). In turn, activated MASPs cleave and activate downstream complement components that eventually neutralize the invading pathogen (Ikeda et al., 1987; Schweinle et al., 1989). MBP is also able to activate the classical and the alternative complement pathways, thus adding additional significance to its host protection role. Furthermore, MBP activation of complement promotes the formation of C3b and C5b fragments that increase opsonization, phagocytosis and the neutralization of pathogens by macrophages (Kuhlman et al., 1989; Schweinle et al., 1989; Stahl and Ezekowitz, 1998). There is some evidence that suggests MBP may initiate phagocytosis by neutrophils and monocytes directly by binding to bacterial cells (Kuhlman et al., 1989; Stahl and Ezekowitz, 1998). MBP compromised individuals are more susceptible to infections, and this emphasizes the importance of MBPs in the host defense response to pathogenic invasion (Stahl and Ezekowitz, 1998; Kerrigan and Brown, 2009). Another endogenous collectin known as mannose receptor (MR) is expressed on macrophage and dendritic cell surfaces (Kerrigan and Brown, 2009). MRs recognize and bind yeasts, mycobacteria and a wide variety of Gram-positive and Gram-negative bacteria (Stahl and Ezekowitz, 1998). Macrophages and dendritic cells, both of which are potent antigen presenting cells (APC) (Stahl et al., 1980; Stahl and Ezekowitz, 1998), phagocytose APC expressed MR bound microorganisms and process the phagocytosed proteins into short peptides that are then presented by MHC class I or MHC class II molecules (Gorelik et al., 2001; Kerrigan and Brown, 2009). Antigen presentation by MHC molecules activates T lymphocytes, and activated T lymphocytes then stimulate the adaptive immune system (Gorelik et al., 2001). Collectins such as MBPs and MRs play active roles in host defense systems against invading pathogens and infection (Kerrigan and Brown, 2009). It is also possible that MBPs and MRs are able to target and neutralize malignant cells due to their altered glycan moieties (Kim et al., 1993; Gorelik, 1994).

Galectin functions

The S-type lectins (galectins), another member of the CTL superfamily, are known to be involved in a wide variety of cellular processes that include pre mRNA splicing, cell growth regulation, cell adhesion, embryogenesis, inflammation, immune function, apoptosis, angiogenesis and tumor metastasis (Barondes et al., 1994; Perillo et al., 1998; Cooper and Barondes, 1999; Rabinovich, 1999; Nangia-Makker et al., 2000;Sharon and Lis, 2004; Rabinovich et al., 2007; Malik et al., in press). Neoplastic progression has been associated with increased galectin-3 expression in malignancies of the head, neck, gastric or anaplastic large cell lymphoma tumors, thyroid and central nervous system (CNS) tumors. However, galectin-3 expression has been shown to be down regulated in carcinomas of the uterus, breast and ovary. This suggests that alterations in galectin-3 expression may affect malignant cell interactions with other normal and malignant cells via their corresponding ligands, and thus affect their local growth potential and their potential to metastasize into other anatomical locations (van den Brule et al., 1994; Schoeppner et al., 1995; Castronovo et al., 1996; Gillenwater et al., 1996; van den Brule et al., 1996; Bresalier et al., 1997). Galectin-3 was also shown to

have anti-apoptotic effects in galectin-3 cDNA transfected human T cell leukemia Jurkat E6-1 cells (Yang et al., 1996; Akahani et al., 1997). The anti-apoptotic effects of galectin-3 are primarily associated with the C-terminus NWGR motif. This anti-apoptotic activity is abolished with a single amino acid substitution, such as glycine 182 to alanine (Yang et al., 1996; Akahani et al., 1997).

In other studies it was reported that some endogenous animal lectins, such as galectin-1 (in humans) and galectin-9 (in mice), have cytotoxic activities and are able to induce thymocyte apoptosis (Wada et al., 1997; Gorelik et al., 2001). Galectin-induced apoptosis of thymocytes has been associated with the physiological selection processes of thymocyte maturation in the thymus (Gorelik et al., 2001). The cytotoxic activities of these galectins are not isolated to thymocytes and are also applicable to malignant cells as well. It was found that recombinant galectin-1 was able to activate apoptosis in several human B lymphoid cell lines, including Burkitt's lymphoma, in addition to T cell Jurkat and MOLT-4 (Perillo et al., 1997).

Optimal signal transmission into cells and adhesion require the clustering of ligands and receptors in most systems. Lectin–carbohydrate interactions are no different and thermodynamically favorable assembly of highly ordered clustering arrays are seen. Galectins bind Gal-β-1-nGlcNAc-R by recognizing the β-gal residue, and the binding affinities to N-glycans are associated with the oligosaccharide content of N-acetyllactosamine (LacNAc) and the GlcNAc branching (Nimrichter et al., 2004; Rabinovich et al., 2007). GlcNAc branching-dependent affinity is important because, as described earlier, cell surface carbohydrates from human and experimental tumors showed that the most prominent alteration in glycoproteins is the presence of larger and extensively branched N-linked β-1,6-GlcNAc oligosaccharides (Dennis, 1991, 1992; Fernandes et al., 1991; Mody et al., 1995; Orntoft and Vestergaard, 1999; Couldrey and Green, 2000). The β-1,6-GlcNAc branched N-glycans are tri- or tetra-antenna oligosaccharides that enable lattice formation through multivalent oligomerization by galectins and other lectins in general (Rabinovich et al., 2007). Lattice formation is preceded by membrane components such as specific glycoproteins, glycolipids and receptors being rearranged into lipid raft microdomains. These lipid raft microdomains are then reorganized by galectin binding during lattice formation. Lattice formation effectively traps receptors at the cell surface and, therefore, regulates the cell surface distribution of these receptors, receptor endocytosis and their activation (Rabinovich et al., 2007). For example, the T cell receptor (TCR) α/β is an N-glycan modified by the enzymatic activity of GlcNAc-TV. Glycosylation of the TCR inhibits random nonspecific clustering of TCRs by binding galectin-3. Multivalent TCR-galectin-3 lattices restrict the lateral movement of TCRs within the plasma membrane and, in turn, restrict TCR aggregation at the immune synapse (Rabinovich et al., 2007). Multivalent TCR-galectin-3 lattices therefore increase the threshold for TCR activation and by doing so regulate immune response (Demetriou et al., 2001; Morgan et al., 2004).

Regulatory T cells over-express galectin-1 and galectin-10 that are vital for the suppressive activity of these cells (Garin et al., 2007; Kubach et al., 2007). It is highly possible that the suppressive activity of regulatory T cells by over-expression of galectin-1 contributes to immune system evasion by malignant cells (Rubinstein et al., 2004). Although, multivalent lattice formation may be one possible mechanism by which galectin–oligosaccharide interaction regulate cellular processes. The exact mechanistic nature of galectin involvement in cellular processes such as cell growth regulation, cell adhesion, embryogenesis, inflammation, immune function, apoptosis, angiogenesis and tumor metastasis remains unclear. However, a wide body of evidence strongly suggests their involvement in many of these cellular processes in normal and diseased states (Platt and Raz, 1992; Barondes et al., 1994; Inohara and Raz, 1995; Perillo et al., 1998; Cooper and Barondes, 1999; Rabinovich, 1999; Nangia-Makker et al., 2000; Saravanan et al., in press).

Carbohydrates in host–pathogen interactions

Many human pathogens utilize cell surface glycans as either receptors or ligands to initiate adhesion and infection (Sharon and Lis, 1989, 2003; Zem et al., 2006; Hyun et al., 2007; Oppenheimer et al., 2008; Magalhaes et al., in press; Mukhopadhyay et al., 2009). *Escherichia coli* (*E. coli*), for example, binds to host mannosides, while influenza virus binds to host sialic acids (Mukhopadhyay et al., 2009). Other strains of *E. coli* have been discovered that demonstrate specificities towards other host cell surface carbohydrate moieties such as galabiose (Gal-α-4-Gal) and NeuAc-α-2,3-Gal-β-3-GalNAc (Khan et al., 2000; Buts et al., 2003). The genital pathogen *Neisseria gonorrhea* specifically binds N-acetyllactosamine (Gal-β-4-GlcNAc, LacNAc), and *Streptococcus pneumonia* specifically binds the pentasaccharide NeuAc-α-3-Gal-β-4-GlcNAc-β-3-Gal-β-4-Glc as well as the internal tetra- and trisaccharides Gal-β-4-GlcNAc-β-3-Gal-β-4-Glc and GlcNAc-β-3-Gal-β-4-Glc respectively. *Pseudomonas aeruginosa* specifically binds fucose (L-Fuc) (Barthelson et al., 1998). Bacteria can discriminate between two identical glycans that differ in only one hydroxyl group (Sharon, 2006). Such host–pathogen interactions are multivalent, and therefore the binding events are of high affinity and suited for host invasion (Nimrichter et al., 2004; Mukhopadhyay et al., 2009). The human immunodeficiency virus (HIV) interacts with the CD4 receptors of $CD4^+$ T cells via its gp-120 glycoprotein (Scanlan et al., 2007). The HIV gp-120 is extensively glycosylated with oligomannose glycans and complex N-glycans that have been shown to interact with galectin-1, thereby stabilizing the attachment of the virus to the target cell (Rabinovich et al., 2007; Scanlan et al., 2007).

Lectin-mediated therapeutics

The concept of lectin-mediated specific drug delivery was proposed by Woodley and Naisbett in 1988 (Bies et al., 2004). Delivery of targeted therapeutics via direct and reverse drug delivery systems (DDS) to specific sites provides numerous advantages over traditional non-targeted therapeutics (Minko, 2004; Plattner et al., in press; Rek et al., 2009). Targeted drug delivery increases the efficacy of treatment by enhancing drug exposure to targeted sites while limiting side effects of drugs on normal and healthy tissues (Minko, 2004; Plattner et al., in press; Rek et al., 2009). Limiting or preventing side effects in treatments is important because side effects typically lead to reduction in dosage, delay in treatment and therapy termination. Furthermore, specific drug delivery increases the uptake and internalization of therapeutics that have reduced cellular permeability (Minko, 2004; Rek et al., 2009). Direct or reverse targeting relies on identifying and utilizing unique moieties of the targeted site while protecting the active (drug) component during the delivery (Fell, 1996). In addition to specific moieties, other parameters such as the target environment and the path taken to reach the target must be considered in tailoring lectin-based DDSs (Minko, 2004; Rek et al., 2009). Drugs passing through the gastrointestinal tract are susceptible to early activation and degradation by the acidic environment and pancreatic enzymes. Alternatively, drugs administrated via the colon are vulnerable to catabolic assault by enzymes of bacterial origin (e.g. dextranase, pectinase, β-D-xylosidase, β-D-galactosidase, amylase, xylanase

and β-D-glucosidase) (Guarner and Malagelada, 2003; Rek et al., 2009). However, it is possible to develop DDSs that take advantage of these bacterial enzymes. For example, a drug core in a fermentable carbohydrate coating, drug–carbohydrate conjugates (prodrugs) and drugs embedded in a biodegradable matrix are all possible designs of drugs that can utilize bacterial enzymes (Sinha and Kumria, 2001; Rek et al., 2009).

Drug targeting

One approach to specific drug delivery as described above is prodrugs. Prodrugs are drug–carbohydrate conjugates that are delivered to the target site in an inactive form and are only activated by specific conditions at the target site. Prodrugs are typically utilized in two forms. The first type of prodrug is broken down within the target cell to form the active therapeutic or therapeutics. The second type of prodrug reacts with two or more compounds to develop the active therapeutic agent under specific intracellular conditions (Minko, 2004; Rek et al., 2009). The production of targeted DDS requires three components: the drug, a targeting moiety and a carrier. The carrier moiety binds all three components of the targeted DDS together and enhances the solubility of the entire complex (Minko, 2004; Rek et al., 2009). Targeted DDSs must meet two important conditions to be effective. First, the therapeutic agent must be protected from degradation or loss of activity, and secondly, the therapeutic agent must be released from the DDS within the target site. Therapeutic agents are typically linked to the DDS via a biodegradable spacer such as the tetrapeptide Gly-Phe-Leu-Gly, which is digested by the enzymatic activity of cathepsin B, thus liberating the therapeutic agent (Kopecek et al., 2000; Kopecek et al., 2001; Lu et al., 2002). Alternatively, the entire DDS may be biodegradable within the target cell (Zeisig et al., 2003). An example of this system would be the combination of horseradish peroxidase with indole-3-acetic acid. Indole-3-acetic acid is oxidized by horseradish peroxidase, thus, forming radical cations that degrade further to form cytotoxic products (Minko, 2004).

Lectin-based drug targeting

Lectin-based targeting of DDSs may be accomplished via two mechanisms (Fig. 2): direct lectin targeting and reverse lectin targeting (Plattner et al., in press). In direct lectin targeting, the DDS has carbohydrate moieties that are recognized by endogenous cell surface lectins. In reverse lectin targeting, the DDS has exogenous lectins that recognize endogenously synthesized carbohydrate moieties on glycolipids and glycoproteins (Bies et al., 2004; Minko, 2004). Recall that human and experimental tumors display increased levels of N-linked β-1,6-GlcNAc oligosaccharides (Dennis, 1991; Fernandes et al., 1991; Dennis, 1992; Mody et al., 1995; Orntoft and Vestergaard, 1999; Couldrey and Green, 2000). This N-glycan would be an ideal moiety in reverse lectin targeting anti-cancer DDSs.

Intravenous administration of anti-cancer chemotherapy reagents produces severe tissue and organ damage due to cytotoxic effects on normal cells. Lectin-based DDSs could be greatly beneficial in cancer therapy, not only due to their specific binding abilities, but also their cytotoxic and apoptosis inducing potentials (Kim et al., 1993; Gorelik, 1994; Mody et al., 1995; Ma et al., 1999; Minko, 2004; Thies et al., 2005; Plattner et al., in press). Some lectins also have mitogenic potential. For example, lectins such as *Phaseolus vulgaris agglutinin* (PHA-L) are mitogenic to non-cancer human colon cell line CRL-1459, while cytotoxic to human colon cancer cell line CCL-220 at 1 μg/ml within 48 h of incubation (Mody et al., 1995; Gorelik et al., 2001; Sharon and Lis, 2004; Heinrich et al., 2005; Petrossian et al., 2007). Cytotoxicity of lectin-based DDSs may be exploited by two mechanisms. One mechanism would involve a non-toxic lectin conjugated to a drug which will become toxic upon activation within the target cell. The second mechanism involves using a toxic lectin that would function as a homing moiety as well as a toxic agent via apoptosis induction (Kim et al., 1993; Minko, 2004; Heinrich et al., 2005). The limitation of the second mechanism is the difficulty in identifying a lectin that would specifically be toxic towards the target cell.

Mistletoe lectin I (ML-I) is a potent antitumor cytotoxic lectin that exerts its effects by protein synthesis inhibition with high efficacy (Mody et al., 1995). Mistletoe lectin extracts, ML-I, ML-II and ML-III, have been used in European countries as experimental supplements for breast cancer therapy (Heinrich et al., 2005; Thies et al., 2005). ML-I was shown to be more toxic towards human MV3 melanoma cells *in vitro* than ML-2 or ML-3. ML-I may potentially be considered as a lectin that meets the criteria for the second mechanism since it has been used in breast cancer therapy and has been shown to be cytotoxic (Mody et al., 1995; Thies et al., 2005).

Efforts have also been made to synthesize lectin–monoclonal antibody conjugates that can specifically bind to target tumor cells and induce cytotoxic effects (Mody et al., 1995). In this system the lectin is the toxic entity and the antibody is a monoclonal tumor-specific antibody. The hope here is that virtually any tumor can be neutralized by using tumor-specific monoclonal antibodies. The toxic lectins typically used are plant lectins such as ML-I or the A-chain of ricin (Tonevitsky et al., 1991; Paprocka et al., 1992).

Carbohydrate-based vaccines and anti-adhesion therapeutics

Carbohydrate-based therapeutics is by no means a modern biomedical concept or application. Honey, for example, has been

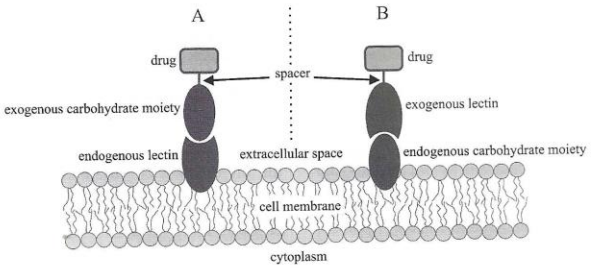

Fig. 2. Schematic illustration of direct lectin targeting (A, left) and reverse lectin targeting (B, right). Illustration prepared by Haike Ghazarian using Corel Draw X4.

utilized for thousands of years as traditional medicine to treat microbial infections and, more recently, gastrointestinal disorders, the common cold, burns, skin ulcers, cataracts, infected wounds and asthma (Lee et al., 2008; Ferreira et al., 2009; Pourahmad and Sobhanian, 2009). Honey is a complex mixture of roughly 200 substances that include carbohydrates, proteins, organic acids, minerals, phenolic acids, enzymes, vitamins, flavonoids and other phytochemicals (Ferreira et al., 2009). Honey is a potent antimicrobial substance with antagonistic activity against pathogenic organisms such as *E. coli*, *Staphylococcus aureus* and *P. aeruginosa*. Manuka honey, for example, has been reported to have antimicrobial activity against multi-drug resistant pathogenic bacteria such as *S. aureus* and *Helicobacter pylori* (Lee et al., 2008). The antimicrobial activity of honey, in addition to other active substances, has been associated with the presence of hydrogen peroxide and minerals such as iron and copper that may contribute to the formation of highly reactive hydroxyl groups (Lee et al., 2008; Ferreira et al., 2009). However, complex carbohydrates found in honey may also contribute to the antimicrobial activity of honey. Complex carbohydrates such as the trisaccharide D(+)melezitose (α-D-glucopyranosyl-β-1,3-fructofuranosyl-α-glucopyranoside), found in honey in concentrations of up to 3.4 mg/g, were shown to be potent inhibitors of yeast-Con A bead-binding system at low concentrations (Aso et al., 1960; Zem et al., 2006; de la Fuente et al., 2007).

Anti-adhesion therapy

As discussed in section "Carbohydrates in host–pathogen interactions", many human pathogens utilize cell surface glycans as either receptors or ligands to initiate adhesion and infection (Kyogashima et al., 1989; Sharon and Lis, 1989, 2003; Thankavel et al., 1999; Zem et al., 2006; Hyun et al., 2007; Oppenheimer et al., 2008; Mukhopadhyay et al., 2009; Rek et al., 2009). Therefore, using specific carbohydrates or their analogs to interfere with the pathogen lectin–host carbohydrate interactions may prevent and treat microbial infections or diseases (Fig. 3). This is precisely the goal of anti-adhesion therapy (Zopf and Roth, 1996; Karlsson, 1998; Kelly and Younson, 2000; Sharon and Ofek, 2000; Ofek et al., 2003a,b). Anti-adhesion therapy offers many advantages over conventional chemotherapies including efficacy, reduction of multiple side effects and environmental sensibility (Sharon, 2006). Many anti-adhesion carbohydrates are found as normal constituents of our diets or endogenously (Kontiokari et al., 2001; Morrow et al., 2005; Newburg et al., 2005; Sharon, 2006; Sinclair et al., 2008). Drugs using these compounds may not be safe and their safety is yet to be determined. Human milk is abundant in oligosaccharides that have inhibitory properties against surface lectins of numerous bacteria. Fucosylated oligosaccharides such as Fuc-α-2-Gal-β-4-GlcNAc are effective inhibitors of adhesion between *Campylobacter jejuni* and human cells. Infants that are breastfed with milk containing elevated levels of these oligosaccharides suffered diarrhea less frequently than those fed with milk containing low levels of these oligosaccharides (Morrow et al., 2005; Newburg et al., 2005; Sinclair et al., 2008). Sinclair et al., (2008) demonstrated the inhibition of cholera toxin binding to the GM1 receptor by sialyloligosaccharides (SOS).

Evidence from non-human cases also support carbohydrate-based anti-adhesion therapies. It was found that new born calves given lethal doses of *E. coli* K99 (F5) were cured by drinking water enriched with glycopeptides prepared from cow plasma non-immunoglobulin glycoproteins (Mouricout et al., 1990). However, difficulties with carbohydrate-based anti-adhesion therapies remain. Several issues that need to be addressed are: development of more potent inhibitors, expression of multiple lectins with diverse specificities by bacteria that may require multiple carbohydrates for inhibition and the low affinity of free carbohydrates for microbial lectins that may be overcome by polymeric carrier–carbohydrate conjugates (Sharon, 2006).

Other agents besides carbohydrates may also be used in anti-adhesive therapies (Rek et al., 2009). Monoclonal antibodies raised against microbial cell surface carbohydrate determinants complementary to host cell lectins will also inhibit attachment of the pathogen (Sharon, 2006). Antibodies are proteins (polypeptides) and may yet offer another anti-adhesive agent. Natural and synthetic polypeptides do exist that have demonstrated specific

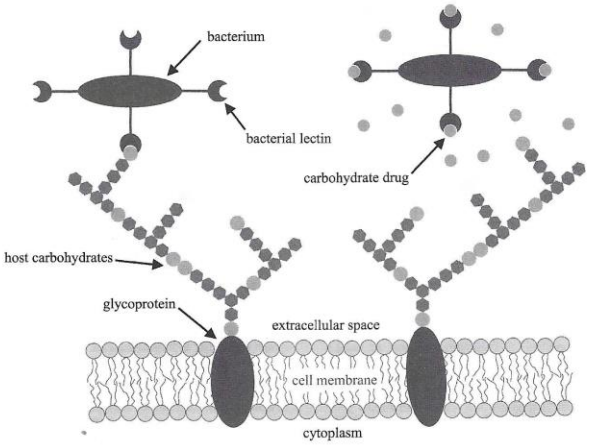

Fig. 3. Schematic illustration of bacterial lectins binding to cell surface glycans of a host cell prior to infection (left) and specific carbohydrates or their analogs interfering with the bacterial lectin–host carbohydrate interactions (right). Illustration prepared by Haike Ghazarian using Corel Draw X4.

binding potentials (Hyun et al., 2007; Ajesh and Sreejith, 2009). Hyun et al., (2007) found that synthesized peptides had increased specificities when compared to natural lectins. The synthetic peptides, however, had binding affinities that were an order of magnitude weaker than those of natural lectins. Most naturally occurring peptides are not and cannot be used as therapeutic agents because of toxicity against mammalian cells, low tissue binding and penetrability, high cost and susceptibility to proteolytic degradation (Ajesh and Sreejith, 2009). Further investigation is required to establish a complete list of natural and synthetic peptides that may be used in anti-adhesion therapies.

Carbohydrate-based vaccines

Carbohydrate-based vaccine development has had a long history; dating back to the early 1920s, but it has not received much attention for the better part of the twentieth century due to efforts being focused on chemotherapeutic and antibiotic therapies (Vliegenthart, 2006; Abdel-Motal et al., 2009; Hecht et al., 2009). The steady rise in antibiotic resistance has revived interests in carbohydrate-based vaccines once again. One issue with carbohydrate-based vaccines is that polysaccharides generally induce poor immunogenic response in normal individuals and especially in high risk groups such as neonates, children two years or younger, the elderly, chronically ill individuals and immuno-compromised individuals such as HIV and chemotherapy patients (Vliegenthart, 2006; Oppenheimer et al., 2008). To overcome this weak immune response, even when specific disease carbohydrate antigens are used in vaccine development, researchers have developed multi-component vaccines (including a three component vaccine), thus strengthening the immune response (Galonic and Gin, 2007; Abdel-Motal et al., 2009; Hecht et al., 2009). The three components are: a carbohydrate antigen, an immunocarrier protein such as keyhole limpet hemocyanin (KLH) and an immunological adjuvant such as QS-21A (Vliegenthart, 2006; Galonic and Gin, 2007; Hecht et al., 2009). The carbohydrate antigen–KLH complex is processed by antigen presenting cells, and the processed antigen is then presented to T cells. This T cell activation results in a strong T cell response with cytokine release that stimulates antibody production. The immune response generated here is directed not only towards the KLH immunocarrier protein, but also towards the weakly immunogenic carbohydrate antigen (Vliegenthart, 2006; Galonic and Gin, 2007; Hecht et al., 2009). The immunological adjuvant QS-21A is non-immunogenic on its own; however, when co-administered with the carbohydrate antigen–immunocarrier protein complex, it further enhances the immune response (Kensil et al., 1991; Helling et al., 1995; Ragupathi, 1996; Hecht et al., 2009). All three components of carbohydrate-based vaccines, however, must be safe for human administration (Vliegenthart, 2006; Hecht et al., 2009).

Advances in technology make it possible to synthesize complex carbohydrates and produce designer immunogenic complexes (Vliegenthart, 2006; Galonic and Gin, 2007; Scanlan et al., 2007; Oppenheimer et al., 2008; Hecht et al., 2009). Carbohydrate vaccines that utilize these new developments offer innovative approaches to human disease mitigation (Galonic and Gin, 2007; Hecht et al., 2009).

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DATA (93)

student co-authored full length peer-reviewed papers: 60

student co-authors: 208

Average # students on these papers: 3.5

CAREER OUTCOMES OF SOME LAB ALUMNI (who reported their careers to Steve) (93)

Ph.D.s: 52

M.D./M.D.-Ph.D.s: 62

Dentists: 33

Pharmacists: 17

Scientists in research and education: 97

Lawyers: 2

ACTUAL DATA ON CAREER OUTCOMES OF SOME LAB ALUMNI UPDATED TO 2021. THIS IS ONLY A FRACTION OF CAREER OUTCOMES AS IT INCLUDES ONLY THOSE WHO REPORTED TO STEVE. This indicates enhanced science workforce in this little sample and correlates with lab mentoring that may or not be causative. The Celina Barba Simic story in this paper suggests causation. * names are some of those who continued to complete a Masters degree with Steve.

John Scordato, Ph.D. USC *
Paul Aunchman, Environmental Pollution , Health Inspector *
Bill Childress, ran computer firm *
Chris Capelle, M.D. *
Richard Behringer, Ph.D., Professor *
Steve Sorenson, D.D.S. *
Bill Saxton, Ph.D. U Colorado, Professor *
Peter Thompson, M.D. *.
R. Clay Steiner, M.D. *
Mina Alikani, Lead Specialist, Cornell In vitro fertilization program *
Stanley Liang, Ph.D., Harvard *
Karen Simpson, USC Dental School *
Julie Gorchynski. M.D., Clinical Medicine Director, UC Irvine now Texas, Professor, BIG CSUN DONOR *
Elias Azzam, Research Associate *
Susan Crowther, Professor, College of the Canyons *
Larry Tawa, M.D. *
Sheryl Fulop, D.V.M. *
Heber Becker, UCLA Medical School *
Karen Berg, M.D. *
Dana Nojima, Ph.D., U Minnesota *
Phil Patenaude, K-12 teacher *
Arunas Banionis, M.D. *
Pradnya Kuwwadekar, Research Scientist *
Miriam Golbert, Professor, Community College *
Debra Kowal, Forensic Technologist, Community College Instructor *
Helen Fredell, K-12 teacher *
Jerome Puttler, K-12 teacher *
Linda Esmaili, Research Scientist *
Marci Spiegler, Community College Instructor *
Mohsen Saidinejad, Ph.D. pgm *
Greg Bentley, Research Associate *
Alice Stanboli, Biotechnology Research Scientist *
Mehrnoosh Saghizadeh, Biotechnology Research Scientist *
Tanya Borisavljevic, M.D. *
Sandra Matsumoto, Ph.D., U Utah, Industry Scientist *
Ani Issaian, Cal Tech Electron Microscopy Facility Director *

Ron Roque, Pollution Inspector, City of Los Angeles *
Pat Krueger, U.S. Forest Service Scientist *
Valerie Dunn, Research Scientist, Industry *
Michael Daily, M.D. *
Brian Salbilla, Research Associate? *
Norman Lautsch, Research Associate ? *
John Slack, was in med school *
Majid Heydarizadeh, Ph.D. pgm *
Ana Garcia-Flack? *
Mary Keens, Criminologist *
Miguel Rocha, Research Associate *
Bibi Aguero, Research Scientist, Industry *
Tun-yin Joseph Yeh, Ph.D., U Utah *
Cynthia Hochman, D.V.M. *
Vern Traxler, Criminologist *
Jessy Philip, Criminologist *
Virginia Latham, Senior Research Associate *
Pavanjit Chhabra, D.D.S. *
Audra McKenzie, Research Associate *
Paul Narguizan, Ed.D. or Ph.D. USC Professor or Adjunct Professor *
Houman Vaghefi, M.D./Ph.D. Chicago Med *?
Tharenee Sakhakorn, D.D.S.? *
Bernard Hunwick, Ph.D. pgm? *
Vanessa Navarro, M.D. *
Sheri Walker, M.D.
David Khatibi, M.D. *
Lital Kirszenbaum, D.V.M. pgm UC Davis *
Lyla Ngo, Medical School *
Evelyn Soriano, was in Ph.D. pgm
Lily Welty, Ph.D. or Masters pgr UCSB *
Eileen Heinrich, Ph.D. UCLA, postdoc *
Ziba Razinia, Ph.D. pgm Yale, post doc. U Penn *
Hesam Hekmatjou, was in Harvard Dental School
Astrid Hernandez, K-12 teacher
Anna Martinez, Stanford Medical School
Luis Rodriguez, Ph.D. Cornell, Senior Scientist NIH
Monica Tully, K-12 teacher *
Maria Abundis, UCSD Medical School

Juan Carlos Pelayo, UCSF, M.D.
Edward Yamoah, UCSF M.D.
Gayanee Weerasinghe, Johns Hopkins/NIH Ph.D. pgm
Marcella Barajas, U Minnesota Ph.D. pgm
Arash Razi, NYU Dental School *
Karina Garcia, West Virginia U Masters pgm
Nasim Monajemi, M.D. pgm
Claudia Garcia, Ph.D. Harvard, Senior Scientist
Sabino Herrera, D.V.M. UC Davis
Karen Brannon, M.D./Ph.D. pgm U Kansas
Celina Barba, M.D. Stanford Medical School, Emergency Room Physician, co-director Emergency Department
Rhodelio Cruz, Ph.D. UC Berkeley *
Jeanette Ducut, Ph.D., UCSD, postdoc
Karolin Abedi, Pharmacy School
Rashad Riman, Dental School
Stephanie Gipson, Criminologist
Juan Sosa, Medical School
Melena Grigorian, Phg.D. pgm
Edna Francisco, Science Writer
Liat Attas, Medical School
Talin Haritunians, Ph.D. pgm
Cecil Addy, M.D.
Krystal Jarvis, Laboratory technician*
Linda Brunick, Ph.D. pgm
Monica Londono, Research Associate
Mike Kaliko, Chiropractic pgm *
Maribel Alvarez, Ph.D. pgm UC Irvine
Karineh Petrossian, Ph.D. pgm City of Hope *
Jennifer Nnoli, Ph.D. pgm, Sloan Kettering
Rashad Riman. Dental School
Christine Le, Dental School *
Arjang Naminik, Dental School *
Arbi Keshishian, Dental School *
Evelin Adamian, Dental School
Rabin Ebrahimi, Pharmacy School
Souren Basmadjian, Pharmacy School
Mike Astete, Dental School
Jehan Murugaser, M.D.

Stacy Tanaka, K-12 Teacher
Ignacio Saldain, K-12 Teacher*
Oliver Badali, Cosmetics Scientist
Rowena Bada, Nurse
Azalia Contreras, Community College Instructor *
Pouria Parsa, M.D.
Massoud Agahi, M.D.
Mary Haghi, M.D., Pediatric Endocrinologist
Neema Oroomchi, Medical School
Ardy Khou, Dental School
Sina Samie, Medical School
Anush Margarian, Pharmacy School
Marie Gonzalez, Pharmacy School
Allen Tabibian, M.D., FACC, Cardiologist
Ralph Buoncristiani, D.D.S.
Stephen E. Jones, M.D.
Andy Solkovits, M.D., Assoc. Professor UC Davis
Erica Dent, Master of Health Administration pgm USC
Jenieke Allen, admit.Ph.D. pgm*
Justin Dreyfuss, Ph.D. pgm, USC*
Diana Naderi, admit MD pgm
Brian Idoni, Research Tech II USC*
Margaret Lemell (Aranda), M.D.
Richard Karout, Pharmacy school
Arbi Keshishian, Dental School*,
Tiffany Smith, PA program
Christine Le, Dental School*
Arjang Naminik, Dental School*
William Dalrymple, Osteopathic School of Medicine
Ziba Razinia, Ph.D. Yale, Postodc U Penn*
Earl Sandroff, D.M.D.
Susan Wensel, Monsanto R&D*
Kim Krach, M.D.*
Sokuntheavy So, Research technician
Oliver Badali, Cosmetics industry chemist
Collete Bibayan, admitted 2 pharmacy schools
Vanessa Navarro, M.D., Family Practice San Diego *
Mark Sussman, Ph.D., DISTINGUISHED PROFESSOR SAN DIEGO STATE

Herry Budiyono, Hospital patient analyst*
Claudine Bulan, Cytology Training Program, Wisconsin
Houman Vaghefi, MD, Ph.D, Radiation Oncologist*
Poria Edalat, Dental School
Lauren Michaels, Veterinary School
Basmah Akhter, Pharmacy School
Nareeneh Zadori, Pharmacy School
Eileen Heinrich, Ph.D. UCLA, now staff scientist at City of Hope*
Jordan Vallejo, h.s. summer res 2yrs, Purdue University, mechanical engineering
Niosha Edalat, USC Dental School and Admissions Ambassador
Forooze Rashidi, Instructor College of the Canyons*
Odette Arman, In vitro fertilization clinic embryologist*
Mark Colgin, Clinical laboratory technologist
Drew Edelberg, high school research student, B.S. Berkeley, Ph.D. Program,
solid state physics, Columbia University
Maria Atikyan, Masters in nursing program
Alexandra Mokh, Instructor/Professor, LA Valley College*
Pam Klein, M.D., Vice President Clinical Development at Genentech
Tina Askari, research associate*
Hurig Katchikian, medical school*
Marianna Muradyan, pharmacy school USC
Lana Darghali, pharmacy school
Lusineh Mirzakhani, admitted to pharmacy school
Evelyn Adamian, dentist
Ofelya Tonyan, accepted Western University of Health Sciences
Jigar Patel, medical school
Jenieke Allen, Ph.D. program Cedars Sinai*
Krystal Jarvis, teacher*
Hamid Davoudi, college teacher, PA program*
Forooze Rashidi, teacher*
Odette Arman, In vitro fertilization embryologist,*
Ronik Khachatoorian,. Ph.D. UCLA, postdoc UCLA
Mirey Qubrosi, Technical Associate, product testing research
Oryla Wiedoeft, EdD, Teacher, Asst. Principal,
Jouliana Davoudi, Dental school USC*
Debrin Yahya-Kashani, CSUN Nutrition Masters program
Yukiko Kanda, Masters program in social work

John Sobhani, research associate UCLA
Tiffany Smith, PA program* USC Keck School of Medicine
Suprita Singh, Ph.D. program Penn State*
Hye Na Kim, research assistant
Ignacio Saldain, HS teacher*
Jung Suh, Amgen quality control analyst
Krystal Jarvis, Research associate*
Careen Khatchitorian, Ph. D pgm, UC Riverside
Marina Hernandez Vergara, K-12 teacher
Ravneet Gill, MD pgm
Hamid Allatabakhsh, dentist- periodontist
Anita Aloian, Optometry pgm, Western University
Eddie Karabidian, USC Dental School*
Hamid Davoudi, PA program*
Pam Klein, M.D., Oncologist, Head Biotechnology company
Noreen Warner, PA program
Lenny Mayorga, Lenny, USC Dental School
Edmund Petrossian, Med School
Nomiki Kolettis, Ph.D. pgm UC Riverside, now research associate
Yukiko Kanda Petrus, Masters of Social Work pgm CSUN
Anasheh Ghazarian, research technician
Sokunttheavy So, research technician
Hiensen Hiesmantjaja, Med School
Armin Sarkissian, Med School
Ivette Ramos Ortega, med school, 9-19-14, remarkable testimonial sent
Virginia Hutchins Carroll, laboratory manager College of the Canyons *
Samantha Arvizu, technical associate
Mai Phan, csun M.S.pgm, research associate
Gayani Weerasinghe, passed bar, patent attorney
Miriam Golbert, Chair, Biology Department, College of the Cabnyons*
Heghush Aleksanyan, csun M.S. pgm, teaching assoc, medical school
Alex Kandel, law school – Berkeley
Helen Chun, Ph.D. and postdoc UCLA, Assoc.Prof., Chair Biology, CSU Dominguez Hills
Karina Garcia, Ph.D. program, history

6. Pre-College

As career objectives are often decided before students enter college, we have published a pre-college journal for 25 years that showcases research by hundreds of pre-college students and their teachers [1]. In addition, we have developed a pre-college research poster symposium that gives hundreds of students the opportunity to showcase their research. Advanced college undergraduates review the posters and congratulate the youngsters who receive medals and certificates. All participating students receive medals and certificates for great efforts. This is not like a science fair where only a few kids are "winners." All poster presenters here are "winners" and this is the pre-college component to help improve the science workforce at an early age [1]. Here is a Commentary I wrote for NSTA Reports October 2019 read by hundreds of thousands of NSTA members that explains our Pre-college program.

The Value of Recognizing the Efforts of All Science Students By Steve Oppenheimer. Current education research (2) has shown that precollege science experiences substantially increase the number of students choosing a science major in college. However, science fairs usually select a relatively small number of winners from hundreds of participants, leaving most with little to show for their efforts, which can diminish those students' future interest. About 35 years ago, I established a research training program for K-12 teachers. After training many teachers in our labs, I developed the Journal of Student Research Abstracts (JSRA) to showcase and reward participating students with published abstracts in a free online journal. All students, not just the high achievers, should be encouraged to do precollege science research, as by the time they reach college, they often have decided on careers. The United States needs more research scientists, so we should encourage many more students, not just high achievers, to fall in love with science. Teachers across Los Angeles and across the U.S.A. submit abstracts on behalf of their middle and high school students to JSRA. Journal editors and teachers rigorously review abstracts, and students have the opportunity to correct any problems. Although this research is conducted by students, scientific rigor is expected. Abstracts document the use of appropriate controls, sufficient replications, and adequate numbers of samples. Accepted abstracts are published in the journal, and student authors receive a print copy of the journal containing their published research. (JSRA is available online at http://bit.ly/2kkE0Et.) One teacher said their students dance with joy upon seeing their work in print.

Center for Cancer and Developmental Biology Pre-College Research Poster Symposium, which also recognizes hundreds of middle and high school student scientists each year. The posters often are based on the reviewed project abstracts submitted to JSRA, and a cadre of advanced senior level university students trained in research science evaluate them. Students conduct their research at their schools and homes, and present their reviewed research in poster form at the symposium, held at California State University, Northridge (CSUN), where they receive medals and certificates recognizing their efforts. This really inspires them to continue in science. Former students who contributed to the journal and participated in the symposium have reported that their siblings "fight" to become involved. Students have been admitted to a spectrum of higher learning institutions, including the California State University system, University of California system, Drexel University, Oxford, Pepperdine, Stanford, Harvard,

Penn State, and the University of Tokyo. Thousands of good precollege science experiences exist that can motivate students to choose science careers. Just having a great science teacher can spark students' interest. Our journal and poster symposium recognize thousands of kids for their research work. A reward like a published abstract or a medal and certificate may be the first and often only recognition from a university many of these students receive. Following the most recent symposium, CSUN Vice Provost Matt Cahn noted, "This is one of those transformative opportunities that we hope all students have." How often do hundreds of students receive university and parental recognition for science research work? The pride that families take in their children's science work provides an extra push for them to choose a science career. These programs are replicable by teachers, schools, and school districts if they wish to encourage many more students to contemplate future science careers. I also suggest that science educators consider urging their middle and high school students to submit research abstracts to JSRA. (Author's note I would like to thank Andrew Weiss, Elizabeth Altman, Mindy Berman, Alvalyn Lundgren, and Helen Chun for their work on JSRA. I have been fortunate to have support from CSUN leadership and staff in launching and running the symposium and the journal). Steve Oppenheimer, professor emeritus, CSUN, has received several awards, including the Presidential Award for Excellence in Science, Mathematics, and Engineering Mentoring and a CSU System Trustees Outstanding Professor award. He is an American Association for the Advancement of Science Fellow and serves as director of CSUN's Center for Cancer and Developmental Biology. He was editor of Elsevier's international journal Acta Histochemica, affiliated with the International Federation of Societies for Histochemistry and Cytochemistry. He has taught, conducted research, and worked with middle and high school students and teachers at CSUN for 48 years .

7. Conclusions

This Mini-Review documents student co-authors and career outcomes and suggests that this open research program is a model for enhancing the science workforce. The White House and NSF honored Steve Oppenheimer with a US Presidential Award for this work, as did the AAAS in electing Steve as a Fellow. The AAAS Fellow designation is a valued research honor that suggests that the student co-authored papers are of high quality. Steve's mentoring program uses advanced undergraduates to help train the newcomers so the job of offering research experiences to large numbers of students is feasible and easy to accomplish as long as motivation and enthusiasm abound. The example of a student, mentored by Steve, who is a Stanford M.D. and co-director of a major hospital's emergency department, provides evidence that this mentoring program can indeed serve as a model for enhancing the science workforce.

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