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Albert M. Wu *Editor*

# The Molecular Immunology of Complex Carbohydrates-3

 Springer

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Albert M. Wu  
Editor

# The Molecular Immunology of Complex Carbohydrates-3

 Springer

*Editor*

Albert M. Wu  
Glyco-Immunochemistry Research Laboratory  
Institute of Molecular and Cellular Biology  
College of Medicine  
Chang-Gung University  
Kwei-Shan, Tao-Yuan 333  
Taiwan  
amwu@mail.cgu.edu.tw

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## **Winifred M. Watkins**

**August 1924-October 2003**

On 3 October 2003, Winifred Watkins died, and even now, I can remember the sadness I felt when I heard the news. Three weeks before her death, I met her at a meeting in Cambridge organised by the Lister Institute in honour of Walter Morgan, who had died earlier in the year. Despite being wheelchair-bound following an earlier stroke, Winifred was still enjoying talking about science. Winifred was not well enough to give her own tribute to Walter but did correct others who strayed from the facts. During lunch, I had the feeling she was saying goodbye to those of us who had worked with her and Walter. I remember laughing as she persuaded Marcela Contreras to push her wheelchair back to the car by the shortest but, for Marcela, most dangerous route, given the height of Marcela's stilettos! That was the last time I saw Winifred. News of Winifred's death, a few weeks later, did not come as a surprise. In many ways, Walter and Winifred were an inseparable scientific team, and their passing within months of each other brought to the end a golden era of research into carbohydrate blood-group antigen structure.

Winifred Watkins was born in London, on 6 August 1924, the younger daughter of a process engraver who was an accomplished amateur painter. She began her schooling in London and, in 1935, was awarded a scholarship at Godolphin and Latymer School, where she was able to pursue her studies of the sciences. During the war, the school was evacuated to the Berkshire. Newbury was a boys' school that had teaching laboratories in which Winifred gained permission to study sciences alongside her male counterparts. In 1940, she returned to London and graduated in 1942 with her Higher School Certificate. The war precluded her entry to university, and she joined the Biochemistry Department of the Lister Institute in Chelsea Bridge Road, London, as a technician. At the time, the Lister was a "hot bed" of scientific ideas and research, and this stimulated her to study at Chelsea College in the evenings to gain her honours degree in chemistry in 1947. During this time, she worked with Walter Morgan on blood-group substances, and in 1944 they produced enough data for her first publication. This seems to have been a

contentious event as she had no degree and was required to have written permission from the directors of the Lister Institute before the paper was accepted. Having learnt from her own earlier experiences, she encouraged her younger technicians to undertake research projects and publish papers, realising the benefit this can bring; many went on to gain their own Ph.D.s. Indeed, my first-ever publication with Winifred was whilst I was a sandwich student, a year before I gained my own undergraduate degree.

In 1947, she began her post-graduate studies at St. Bartholomew's Hospital Medical School, London, with Arthur Wormall, a renowned immunochemist. She studied the action of nitrogen mustards on the immunological properties of proteins. In 1950, she returned as a post-doctoral fellow to work with Walter Morgan at the Lister Institute, and this was the start of their lifelong scientific partnership.

Between 1957 and 1958, she and Walter uncovered the relationships between the H antigen and the ABO system and, using serological and biochemical techniques, described the structure of the ABH and Lewis blood-group antigens. In the late 1950s, Walter and Winifred speculated on the mechanisms involved in the biosynthesis of the blood-group antigens, and this led to the proposal that the products of the *ABO*, *H*, and *Le* genes were glycosyltransferases that transferred terminal sugars from nucleotide sugar donors onto growing oligosaccharide chains. In 1960, Winifred was awarded a Henry Wellcome Travel Fellowship and spent a sabbatical year in Zev Hassid's laboratory at the University of California, Berkeley, where pioneering work on glycosyltransferases was underway. During that time, she was involved with work leading to the discovery of the enzyme lactose synthetase. In 1966, Winifred proposed, without experimental evidence, that glycosyltransferases were responsible for the production of A, B, H, and Le antigens. The pathways predicted helped explain the variation in H antigen levels in individuals with A, B, AB, and O blood types and predicted that individuals from Bombay would lack the  $\alpha$ -2-fucosyltransferase product of the *H* gene. The scheme also explained why secretors of H substance who possessed the *Le* gene would always produce Leb<sup>b</sup>, whereas non-secretors would produce Lea<sup>a</sup>. Over the next 5 years in Winifred's laboratory and in Vic Ginsburg's laboratory in the USA, the appropriate enzymes were found to prove the hypothesis, and by the early 1970s, glycosyltransferase assays were carried out routinely within laboratories. This allowed analyses of rare blood groups and chimeras, tissue distribution studies, and the onco-developmental nature of the antigens. This period was the heyday of the Lister Institute, which was also home to Rob Race, Ruth Sanger, Pat Tippett, and Marcela Contreras—with whom Winifred had many lively discussions and for whom she had an enduring respect.

In 1975, the Lister Institute closed, and after much discussion, Winifred moved with her group to the MRC Clinical Research Centre in Harrow, where she was the only non-medically qualified departmental head, to lead the new Division of Immunochemical Genetics. Their work on glycosyltransferases continued, focusing on localisation, characterisation, purification, and, finally, gene cloning. The underlying causes of blood group ABO, H, and Le anomalies and weak subgroups

were unravelled. Support for the allelic basis of the *A* and *B* genes was found when the group demonstrated the overlapping specificity of the *A* and *B* transferases. Work on fucosyltransferases supported the idea put forward by Rafael Oriol that *H* and *Se* genes were responsible for the production of H antigen on red cells and in secretions, respectively, and demonstrated relationships between some but not all fucosyltransferases. Further research demonstrated specificities of a range of fucosyltransferases and highlighted their roles in leukaemias. Following the production of polyclonal and monoclonal antibodies against the purified *A* transferase and the fucosyltransferases, the work moved into molecular biology, using polyclonal antibodies to screen expression libraries.

In 1984, Winifred's 60th birthday was celebrated with a Biochemical Society meeting in London, which many of her colleagues and friends attended. However, following a very positive quinquennial review, the decision was made to close the Division of Immunochemical Genetics when Winifred retired from the MRC in 1989. The work was curtailed, and the group disbanded. The closure of the Division at the MRC was a bitter blow, particularly as it followed such an excellent review of the research. I am sure she deeply regretted that the work into blood-group antigen biosynthesis did not continue in the UK. Winifred then moved to the Hammersmith Hospital, where she was able to follow up work on fucosyltransferase and sialyltransferase expression in normal white cell maturation and leukaemia. This work continued until the millennium, when Winifred stopped laboratory based research and concentrated on more academic work, until a stroke prevented her from continuing.

During her lifetime, the impact she made in glycobiology and transfusion science can be demonstrated by the awards she received: In 1965, she was awarded the Oliver Memorial Fund award for her work in transfusion science; in 1967, she received the Karl Landsteiner Award of the American Association of Blood Banks; and in 1969, the Paul Ehrlich-Ludwig Darmstadter Medal and Prize. In the same year, she was elected to the Fellowship of the Royal Society of London, and in 1970, she was awarded the William Julius Mickle Fellowship at the University of London. She was presented with the Kenneth Goldsmith Award of the British Blood Transfusion Society in 1986, the Royal Medal of the Royal Society in 1988, the Franz Oehlecker Medal of the German Society of Transfusion Medicine and Immunohaematology in 1989, and the Phillip Levine Award of the American Society of Chemical Pathologists in 1990. She also received an Honorary DSc in chemistry from the University of Utrecht in 1990. She was elected as a member or a fellow to the Royal Society of London (Fellow, 1969), The Royal College of Pathologists (Fellow, 1983), the International Society of Blood Transfusion (Honorary Member, 1984), the Polish Academy of Sciences (Foreign Member, 1988), The Royal College of Physicians (Fellow, 1990), the Japanese Biochemical Society (Honorary Member, 1990), the British Blood Transfusion Society (Honorary Member, 1996), The Royal Swedish Academy of Sciences (Member, 1988), the Academy of Medical Sciences (Fellow, 1998), and the Biochemical Society (Honorary Member, 2000).



On a personal level, Winifred expected absolute commitment to work, and she was both supportive and protective of her staff. I well remember how, when I was a very young doctoral student on my first trip to Canada, she paid for my lunch at the Hilton for the whole meeting to make sure that I wasn't short of money and made sure to keep a "motherly eye" on me. Twenty years later, when her laboratory was closing, she called me over and gave me equipment and materials "knowing I would make good use of them". Winifred had a love of both good food and wine. When she died, I helped clear her flat and found a collection of labels from wine bottles neatly inscribed with the occasion and date with a comment about both the quality of the wine (and the food) and the occasion. These included labels from the meeting when she heard the Lister Institute was closing ("unbelievable" and "frustrating") to one celebrating her 60th birthday ("memorable").

Winifred will always be remembered as a pioneer in glycobiology and blood-group antigen research, one of the most respected scientists in the UK, and one of the most talented women scientists. During her working life, Winifred gave many memorable lectures and was highly respected in her field. With her enthusiasm for her work, she had the ability to make glycobiology fascinating to those with little interest in biochemistry. Winifred was an extraordinary scientist in many respects, succeeding in what was, at a time, essentially a male-dominated area. She was intelligent, determined, and self-motivated. She enjoyed interacting with other scientists, and she had particularly strong ties with Poland through her friendships with Jerzy Koscielak and a number of Polish students who came on sabbatical to the laboratory. She also had friendly links with Albert M. Wu. She participated in two meetings organised by him: Molecular Immunology of Complex Carbohydrates (MICC)-1 (College Station, TX, 1985) and MICC-2 (Taipei, Taiwan, 1999). Winifred contributed with excellent meeting lectures and articles at MICC-2, and moreover, Winifred and Albert published several papers together. Winifred also had strong links with scientists in Sweden, USA, Israel, Japan, and France. Until her first stroke, Winifred continued to attend meetings, thoroughly enjoying simply being part of the science scene and engaging in discussions and debate.

Although it is difficult to separate "Watkins and Morgan", Winifred was, in her own right, a brilliant researcher. When Walter was in his late 80s and worked at the CRC characterising the Sda antigen and elucidating its relationship with the Tamm-Horsfall protein, Winifred was always mindful of his needs. Walter saw Winifred as his protégé and as a highly talented scientist in her own right. He was always anxious that she be recognised as an independent researcher and valued both their academic and personal relationships. For those of us who worked with Winifred, she could be a hard taskmaster; visits to the library, for example, were done on our own time, and holidays were fitted around work, not vice versa. Lectures were practised endlessly, and mistakes were not allowed; preparation was key to the accomplished speaker. Papers were written and re-written until they were perfect, and doctoral theses did not contain a single mistake. On the other hand, she was inspirational, easy to talk to, and happy to share her knowledge and experience. There are still occasions when I realise what a font of knowledge she had. I learnt

much from Winifred, and in many ways, I wish she had lived to see the upsurge in glycobiochemistry research that has taken place over the past 5 years. Those of us who worked with her, knew her professionally, and shared her friendship will always be grateful for the experience.

Pamela Greenwell  
School of Biosciences  
University of Westminster  
115 New Cavendish Street  
London, UK





Four glyco-immune chemists met at the XIII International Symposium on Glycoconjugates in Seattle, WA, on 23 August 1995. From *left*: W.T.J. Morgan, W.M. Watkins, J. Koscielak, and R.W. Jeanloz



*Left*: Dr. W.M. Watkins commented on her talk at the MICC-1, 14 September 1985: “No one was assigned to give a historical perspective of the past except me”  
*Right*: Two cyst glycoprotein pioneers, Drs. E. Kabat (*left*) and W.M. Watkins (*right*), met at a party honoring Dr. Kabat in Seattle, WA, on 31 August 1995



*Left*: Dr. W.M. Watkins as a chair at the MICC-2, 29 August 1999  
*Right*: Dr. W.M. Watkins (*left*) and Dr. A.M. Wu (*right*) in front of Wu’s poster at the XV International Carbohydrate Symposium, Yokohama, Japan, 14 August 1990



European and Taiwanese glyco-immunologists met at the MICC-2 symposium on 31 August 1999. From *left*: Drs. E. Lisowska, M. Lin (Mackay Memorial Hospital), W.M. Watkins, and M. Duk



Dr. P.W. Cheng (*far left*) was teaching Dr. W.M. Watkins (*second from left*) to use chopsticks at the MICC-2 symposium dinner on 29 August 1999. Also pictured: Dr. N. Sharon (*second from right*) and Mrs. N. Sharon (*far right*)



Dr. W.M. Watkins (*left*) with microbial lectin experts, Drs. N. Gilboa-Garber (*middle*) and N.C. Garber (*right*), from Bar-Ilan University, Israel, at the MICC-2 symposium on 30 August 1999





Participants of the Third International Symposium on Molecular Immunology of Complex Carbohydrates (MICC-3)

國際 醣類 分子免疫學 學術會議-3

Institute of Biological Chemistry, Academia Sinica, Taipei, Taiwan, 8-12 July 2007



# Preface

This is the third time I have organized the international symposium on Molecular Immunology of Complex Carbohydrates (MICC), which was held at the Institute of Biological Chemistry (IBC), Academia Sinica, Taipei, Taiwan, 8–12 July 2007, as a satellite meeting of the 19th International Glycoconjugate Organization (IGO) meeting held 15–20 July 2007 in Cairns, Australia. MICC-2 was held at the same place from 28 August to 2 September 1999, after the 15th IGO meeting in Tokyo, Japan. We have arranged two other glyco symposia and three workshops since MICC-2. MICC-2 (*Adv Exp Med Biol* [2001]; 491) was selected as “an excellent textbook” from Kluwer Academic Publishers in 2002. In this MICC-3 book, three quarters of the content are based on lectures and posters of the MICC-3 symposium, and one quarter is from workshops and promotional materials. The book is divided into an Introduction, eight sections, and an appendix.

The Introduction (Part I), “Glyco Experiences”, shares in one essay the serendipity of scientific discoveries in the glycosciences obtained from the lifetime experiences of Dr. Y.C. Lee (Department of Biology, Johns Hopkins University, MD, USA). In the second essay, Noriko Takahashi (Graduate School of Pharmaceutical Sciences, Nagoya City University, Nagoya, Japan) describes 30 years of work devoted to determining the structures of *N*-glycans.

The main text starts with Part II, “Blood Group ABH/Le-related Antigens,” to pay a tribute to the work of three pioneers in this field: Walter T.J. Morgan, Elvin A. Kabat, and – especially – Winifred M. Watkins, to whom this book is dedicated. This section presents the advanced concepts concerning the structure and functions of these antigens. In my comprehensive review on human blood group ABH/i, Le<sup>a,b,x,y</sup>, and sialyl Le<sup>a,x</sup> glycotopes of human ovarian cyst glycoproteins, I begin with the history of the most important findings and continue to our contemporary view.

The interactions of plant, bacterial, and animal lectins with carbohydrates (and proteins) are thoroughly presented in eight contributions to Part III. Recognition intensities of mammalian structural units, ligand clusters, and polyvalency in the lectin–glycan interaction are some of the important issues covered in this section. The review on the ligand selectivity of adhesion/growth-regulatory galectins is a report of our decade-long collaboration with two glyco labs in Munich, Germany. The evidence for various regulatory roles of glycolipids is continuously increasing. Six contributions in Part IV describe the structures and functions of gangliosides



and microbial glycolipids. The physiological roles of other glycoconjugates (glycoproteins, glycans, cellular receptors) in humans, animals, sponges, and bacteria, as well as aging-related alterations of the glycosylation profile in humans, are the subject of eight articles in Part V. The role of carbohydrates as antigens and regulators of the immune response is widely studied in the four reviews included in Part VI. Malignant transformation of cells is associated with profound changes of glycosylation, and some cancer-related glycoforms play a role in cancer development and metastasis. These aspects of the glycobiology of cancer are presented in five articles in Part VII. New methodologies in glycosynthesis and lectin–carbohydrate binding assays, and strategies for treatment as crucial applications, are described in four articles in Part VIII. Three of them present results obtained by Taiwanese research groups.

An appendix is added at the end of the proceedings to correct typographical and structural errors found in MICC-1 (*Adv Exp Med Biol* [1988]; 228) and MICC-2 (*Adv Exp Med Biol* [2001]; 491).

After the MICC-2 symposium, we lost three blood-group pioneers: Drs. Walter T.J. Morgan (October 1900–February 2003), Elvin A. Kabat (September 1914–June 2000), and Winifred M. Watkins (August 1924–October 2003). Drs. Kabat and Watkins have contributed timeless works to the MICC series. Dr. Kabat's obituary was included in the MICC-2 issue, and Dr. Watkins's obituary is included in this issue.

To this day, this series continues to provide valuable knowledge in the field of glycotopes, structures and functions of complex carbohydrates, recognition factors of lectins, biomolecular interactions, and other glycosciences. I hope these proceedings reflect our worldwide connections, including the friendly collaboration of our lab with colleagues in Taiwan, and other parts of the world, especially Poland, Germany, Israel, Belgium, USA, Japan, Italy, England, India, and China.

As a symposium chair, I owe special thanks to our three co-chairs: Drs. S.H. Wu, C.H. Lin, and K.H. Khoo from IBC, who were the actual driving forces for this symposium and to Drs. Y.C. Lee, R. Schauer, and A. Kobata for their important comments and suggestions. I also thank many members of our lab and staff of IBC, as they worked from early morning to late evening for several months. I also wish to thank the director of IBC, Dr. M.T. Tsai, and the president, C.H. Wong, who provided excellent facilities; the National Science Council (NSC), the Ministry of Education, the Foundation for Research and Education of Glycoscience, and the Research Promotion Center for Life Science of NSC for their financial support; and Chang Gung University for Workshops. I also appreciate the help of Amvo Publishing Company in Taiwan, and Drs. E. Lisowska, H.J. Gabius, Z. Yang, and Ms. Y.P. Gong for their assistance in editing this book. Without their efforts, the symposiums, workshops, and publication of these proceedings would be impossible. Thanks again to all contributors and participants.

Tao-yuan, Taiwan  
10 September 2011

Albert M. Wu

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# Contributors

## **Avijit Kumar Adak**

Department of Chemistry, National Tsing Hua University, Hsinchu, Taiwan

## **Kimberly M. Anderson**

Department of Biochemistry, Tulane University Health Sciences Center,  
School of Medicine, New Orleans, LA 70112, USA

## **Sabine André**

Faculty of Veterinary Medicine, Institute of Physiological Chemistry,  
Ludwig-Maximilians-University Munich, Veterinärstr. 13, 80539 Munich,  
Germany

## **Toshio Ariga**

Institute of Molecular Medicine and Genetics, Medical College of Georgia,  
Augusta, GA 30912, USA;  
Institute of Neuroscience, Medical College of Georgia, Augusta, GA 30912, USA

## **Massimo Aureli**

Department of Medical Chemistry, Biochemistry and Biotechnology,  
Center of Excellence on Neurodegenerative Diseases, University of Milan,  
Via Fratelli Cervi 93, 20090 Segrate, Milano, Italy

## **Itschak Axelrad**

The Mina & Everard Goodman Faculty of Life Sciences, Bar-Ilan University,  
Ramat-Gan 52900, Israel

## **Krishna Baksi**

Department of Anatomy and Cell Biology, School of Medicine,  
Universidad Central del Caribe, Bayamón 00960-6032, Puerto Rico

## **Aditi Banerjee**

Department of Biochemistry, School of Medicine, University of Puerto Rico,  
Medical Sciences Campus, San Juan 00936-5067, Puerto Rico

## **Dipak K. Banerjee**

Department of Biochemistry, School of Medicine, University of Puerto Rico,  
Medical Sciences Campus, San Juan 00936-5067, Puerto Rico



**Sipra Banerjee**

Department of Cancer Biology, Cleveland Clinic Foundation, Cleveland,  
OH 44129, USA

**Annick Barre**

Surfaces Cellulaires et Signalisation chez les Végétaux, UMR UPS-CNRS 5546,  
Pôle de Biotechnologie Végétale, 24 Chemin de Borde Rouge,  
31326 Castanet Tolosan, France

**Manju Basu**

Department of Chemistry and Biochemistry, The University of Notre Dame,  
Notre Dame, IN 46556, USA

**Subhash Basu**

Department of Chemistry and Biochemistry, The University of Notre Dame,  
Notre Dame, IN 46556, USA

**Veer Bhavanandan**

Department of Bioengineering, Center for Glycosciences and Technology,  
The Biodesign Institute, Arizona State University, Tempe, AZ 85287, USA

**Jean-Jacques Bono**

Surfaces Cellulaires et Signalisation chez les Végétaux, UMR UPS-CNRS 5546,  
24 Chemin de Borde Rouge, 31326 Castanet Tolosan, France

**Alexandre M. J. J. Bonvin**

Department of NMR Spectroscopy, Bijvoet Center for Biomolecular Research,  
Utrecht University, Padualaan 8, 3584 CH Utrecht, The Netherlands

**Sarmila Chandra**

Kothari Medical Centre, 8/3, Alipore Road, Kolkata, 700027, India

**Bishnu P. Chatterjee**

West Bengal University of Technology, Salt Lake, 700064, Kolkata, India

**Guo-Yun Chen**

Department of Molecular Pathology, Aichi Cancer Center, Nagoya  
464-8681, Japan

**Huan-Yuan Chen**

Department of Dermatology, University of California, 3301 C Street, Suite 1400,  
Sacramento, CA 95816, USA

**Hui-Li Chen**

Key Laboratory of Glycoconjugate Research, Ministry of Health,  
Department of Biochemistry, Shanghai Medical College, Fudan University,  
Shanghai 200032, China

**Szu-Ting Chen**

Department of Microbiology and Immunology, Institute of Microbiology  
and Immunology, National Yang-Ming University, Taipei, Taiwan