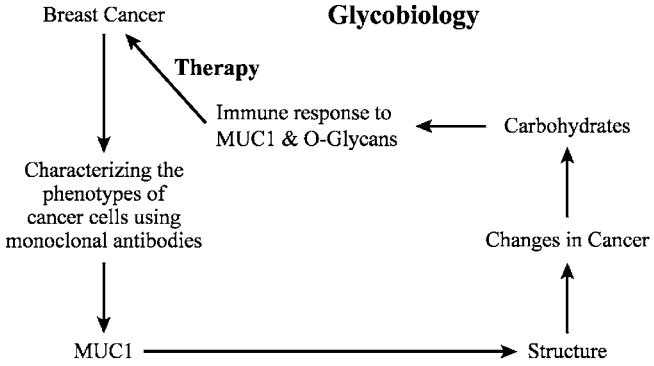
Glycoconjugate Journal 18, 839–840, 2001

Letter for Joyce

Dear Joyce,

I am most pleased to have been asked to write a letter in your honor for this special issue of Glycobiology of Cancer. At a recent NIH meeting on "Carbohydrates and Cancer," Joyce described her development into a glycobiologist as a progression from breast cancer to glycobiology and showed the following diagram:



Describing Joyce is to follow this scientific journey, where she has made a substantial impact on each of the stops on this trip. It was started by her interest in breast cancer. In order to characterize the mammary gland cell type from which breast cancers developed, Joyce developed monoclonal antibodies to the human milk fat globule (HMFG) and to mammary cancer cell lines and used these monoclonal antibodies to identify particular cell types. It is notable that the paper by Köhler and Milstein describing monoclonal antibodies was published in 1976 and by 1979 Joyce had developed and characterized HMFG-1, a monoclonal antibody that we now know recognizes the core protein of the mucin MUC1. A quarter of a century later, in 2004, the results of the Phase I trial for use of HMFG-1 in the treatment of ovarian cancer will be known. At the same time Joyce's group developed monoclonal antibodies to keratins and showed that keratins 8, 18, and 19 and MUC1 were expressed by lumenal epithelial cells and by mammary gland adenocarcinomas, suggesting that the cancer was arising from lumenal cells, a conclusion that has been upheld through the years. Keratins 5 and 14 are characteristic of myoepithelial cells and not expressed by most breast cancers. These expression patterns are still used today to enable scientists to identify what cell types they are studying.

Characterization studies using HMFG-1 and the second antibody in the series, HMFG-2, led to the puzzling result that the protein recognized by these antibodies revealed different sizes in different individuals. A variety of antibodies developed by other investigators using tumors from many different epithelial tumors exhibited similar characteristics. The polymorphism puzzle was solved by gene cloning. In the meantime, monoclonal antibody studies in Joyce's lab showed the very high level of expression of the reactive protein in tumors.

We set out to clone the gene for the protein recognized by these monoclonal antibodies in 1984. Believing at the time that HMFG-1 and HMFG-2 recognized carbohydrate structures, we purified the protein from human breast milk, deglycosylated it, and a new monoclonal antibody called SM-3 (for stripped mucin-3) was generated against the core protein. Cloning led to the first description of a mucin core protein, which was called polymorphic epithelial mucin, PEM. The characteristic structural feature of PEM was the presence of from 30 to greater than 90 tandem repeats of 20 amino acids which comprised much of the extracellular domain of this molecule. Tandem repeats contain a large frequency of serines and threonines to which the *O*-linked carbohydrates are attached and are characteristic of all 15 identified mucins. The presence of the tandem repeats give mucins their structural polymorphisms. Hence, the name polymorphic epithelial mucin was changed to MUC1 (mucin1), the intent being to move to a more distinctive name once we understood the function of this protein. The first papers characterizing MUC1 were published in 1987 in PNAS and Nature. Fifteen years later we are still struggling with the function of MUC1.

The unique pattern of reactivity by the SM-3 antibody led to the conclusion that MUC1 was aberrantly glycosylated in tumors. SM-3 reacted with a wide variety of adenocarcinomas, but showed minimal reactivity with normal or lactating breast tissue. The seminal paper describing SM-3 was published in 1987 and followed the next year with a comprehensive study on SM-3 reactivity in multiple tumor types. Joyce and others and especially Joy Burchell, who has worked with Joyce since the development of the

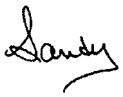
first monoclonal antibodies, have characterized the underglycosylation of the MUC1 core protein that occurs in cancer, showing the presence of an increased number of sialylated core-1 structures, a decrease in branching structures, and a concomitant lack of the core-2 β1,6 GlcNAc transferase enzyme needed to synthesize these branches.

The underglycosylation of the core protein in cancer exposed unique epitopes that were recognized by both the humoral and cellular arms of the immune system, leading to the idea of using MUC1 as a potential immunotherapy target. Joyce developed a transgenic mouse expressing human MUC1 for use in preclinical immunotherapeutic studies and has participated in clinical studies using MUC1 and novel carbohydrate epitopes on MUC1 as immunogens. She has carried this idea forward and involved many European research groups by writing and receiving a series of large collaborative European Union grants to develop glycosylated forms of MUC1 for use as immunogens in preclinical and clinical trials.

Joyce has made a huge impact on glycobiology, especially in relation to mucin biology and carbohydrate alterations in cancer. She has been a leader in the field since developing some of the first mucin monoclonal antibodies. She had the foresight to establish biannual workshops starting in 1990, which initially were to characterize the many antibodies to MUC1 and mucin carbohydrate structures that had been described. The workshops (known to everybody in the field as "The Cambridge Meetings") moved away from antibody characterization and into mucin biology, structure, expression, function, glycosylation, and immunology. These meetings have served the mucin community well, enabling us to keep abreast of the expansion in information about mucins and to encourage interactions and collaborations. Joyce is fearless in her approach to science. She will be stopped by nothing to achieve her goal. Learning from her has been a wonderful experience for me and many others. She gave the freedom to pursue ideas and the means by which to do so, presenting always an original and innovative mind.

Thank you for all that you gave to me.

Most sincerely,



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