GLYCOCONJUGATION: AN EFFECTIVE STRATEGY FOR VACCINATION

Reported by Preston Hills-Rieck March 29, 2018

INTRODUCTION

Vaccines remain one of the most promising therapeutics in preventing infectious diseases associated with pathogenic microbes. Capsular bacteria are known to express unique polysaccharide structures on their cell surfaces that serve many biological functions. Carbohydrates form a capsule around microbes to prevent desiccation and aid in evading a host's immune system. These structures contribute to three different mechanisms for avoiding detection by the immune system: (a) hide from surveilling immune cells of a host organism through their adhesive properties; (b) mimic existing molecular structures in a host organism; (c) disrupt the immune systems' complement pathway from clearing a bacterial infection by preventing phagocytosis via macrophages and other antigen-presenting cells.[1] Microbial cell surfaces' are comprised of tightly ordered repeating polysaccharide units that define the chemically nature of an organism. Additionally, recent advancements in cancer biology has led to understanding of the tumor "glyco-code" which can be exploited to create vaccines that render tumor cells recognizable as foreign invaders by the host immune system (Figure 1).[2,3] These tumor-associated carbohydrate antigens (TACAs) can be linked to hydroxyl groups of serine or threonine that are present on surface proteins (glycoproteins) or conjugated to ceramide lipids that are anchored to the lipid bilayer through hydrophobic interactions (glycolipids). TACAs are useful targets for anticancer vaccines due to their low abundance levels on normal cells and high levels of expression on tumor cells.[3]

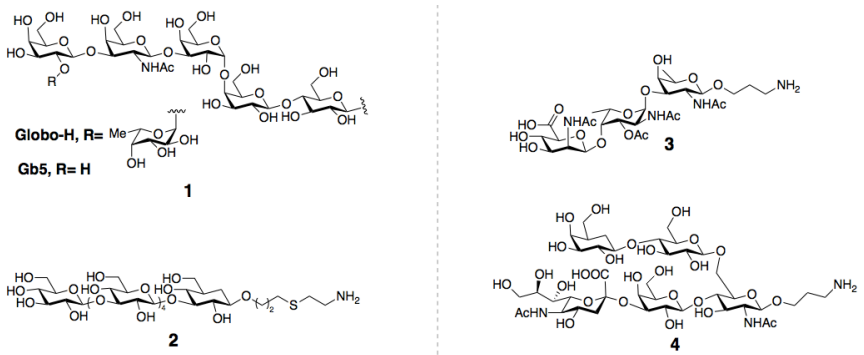

Figure 1: Synthetic carbohydrates from Breast/Prostate tumors (1), C. albicans (2), S. aureus type 5 (3), and GBS type III (4).

GLYCOCONJUGATE VACCINES

Polysaccharides represent an optimal target for deriving highly specific antibodies and cytotoxic T-cells against foreign invaders of the host. Even though carbohydrates are known for endowing antibodies with great avidity and affinity properties they are still poorly immunogenic. However, phagocytosis of the glycoconjugate vaccine by antigen presenting cells (APC), followed by intracellular digestion, and molecular presentation of the antigen via the major histone complex I or II provide T-cells with epitopes for pathogen recognition. T-cells can induce the maturation of carbohydrate specific plasma B-cells via T-helper cells and cytokines (Figure 2).[9] This revolutionary phenomenon that an immunogenic carrier protein can be conjugated to a non-immunogenic molecule to elicit T-cell and B-

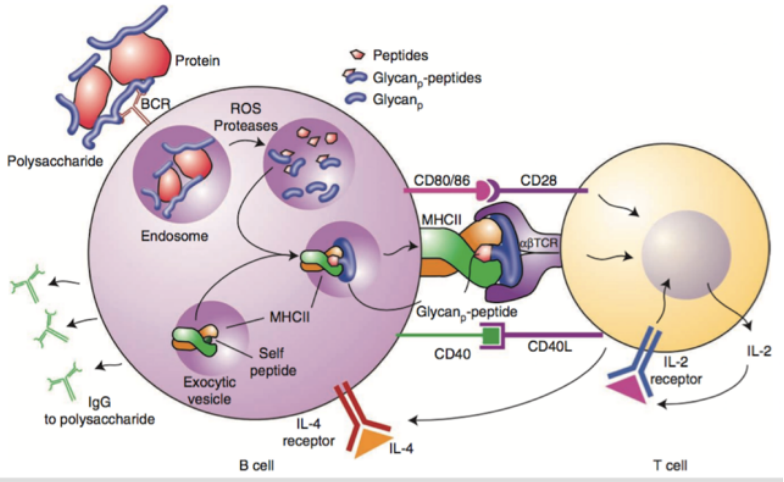

Figure 2. Novel mechanism for glycoconjugate vaccine activation of the adaptive immune response

cell mediated protection engendered the development of glycoconjugate vaccines leading to the development of the first-in-class glycoconjugate vaccine for *Haemophilus influenzae* type b (Hib) approved in 2004 for use in Cuba.[2,4]

The field of carbohydrate chemistry has received a lot of attention with the development of the glycoconjugate vaccines and novel strategies for anticancer therapeutics that target the unique polysaccharide structures of tumor cells.[1,4] Chemical synthesis of complex carbohydrates usually requires extensive multistep reactions and expertise owing to the difficulty associated with achieving stereocontrol of the 1,2 cis-linkages between sugar molecules. Carbohydrate assembly has been largely achieved through one-pot glycosylation synthesis via three strategies: (1) a chemo-selective approach that exploits the reactivity of the anomeric leaving group; (2) a chemo-orthogonal synthesis that uses specific conditions to tune the activity of the anomeric substituents; (3) an iterative synthesis strategy that pre-activates the sugar donor before addition of the subsequent carbohydrate acceptor.[5] Furthermore, conjugation of antigenic proteins/peptides to carbohydrates is traditionally achieved by exploiting the reactive residues inherent in proteins (thiols and amines). Traditional chemical biology strategies for thioalkylations, thiol-maleimide reactions, and reductive aminations are amongst the most common ways of appending carbohydrate moieties onto proteins. The exponential increase of effort towards developing carbohydrate chemistry and bioconjugation techniques has allowed scientists to explore the principles that dictate the efficacy and safety of glycoconjugate vaccines.

HIGHLIGHTS OF GLYCOCONJUGATE VACCINES

Carbohydrates are highly abundant on bacterial, viral, fungal, and tumor cells that evade the human immune system but due to their specificity for cellular identity they offer an attractive opportunity for vaccine therapeutics.[9] Systemic fungal infections are prime candidates for vaccines due to the limited availability, efficacy, or safety of antifungal drugs. Glycoconjugate vaccines offer a novel approach to treating/preventing fungal infections as demonstrated by Novartis Vaccines & Diagnostics Research Center with the development of a vaccine that elicits an adaptive immune response in mice against *C. albican.*[6] Additionally, viral pathogens and cancer are notorious for being difficult to treat with traditional small molecule drugs but vaccines may provide a solution. The impressive work of Dr. Gavin Painter's lab in developing two glycoconjugate vaccines, a universal vaccine against influenza A and melanoma-associated tumors, that utilize an α-Glactosylceramide adjuvant to elicit a NKT-cell mediated immune response.[7,8] Likewise, the Memorial Sloan-Kettering Cancer Center has made substantial contributions in anticancer vaccination with an enzymatic synthesis of a glycoconjugate vaccine that is in phase III clinical trials for treating metastatic tumors.[10] Ongoing efforts to determine the efficacy, safety, and dosing of these vaccines will ultimately decide their fate as potential therapeutics. However, glycoconjugate vaccines will provide scientists with the opportunity to probe the immune system to unravel the complexities that govern T-cell independent/dependent mediated protection to provide more effective vaccines in the future.

(1) Berti, F.; Adamo, R.; *ACS Chem. Biol.* **2013**, *8*, 1653-1663.
(2) Adamo, R.; *Acc. Chem. Res.* **2017**, *50*, 1270-1279.
(3) Feng, D.; Shaikh, A. S.; Wang, F.; *ACS Chem. Biol.* **2016**, *11*, 850-863
(4) "2/Vaccine Immunology." Vaccines, by Stanley A. Plotkin et al., 6th ed., Elsevier, **2013**, pp. 16–34.
(5) Zhu, X.; Schmidt, R. R.; *Angew. Chem. Int. Ed.* **2009**, *48*, 1900-1934.
(6) Adamo, R.; Tontini, M.; Brogioni, G et al.; *J. Carbohydr. Chem.* **2011**, *30*, 249-280.
(7) Anderson, R. J.; Li, J.; Kedzierski, L.; Painter, G. F. et al.; *ACS Chem. Biol.* **2017**, *12,* 2898–2905.
(8) Anderson, R. J.; Compton, B. J.; Painter, G. F. et al.; *Chem. Sci.* **2015**, *6*, 5120-5127.
(9) Avci, F. Y.; Li, X.; Tsuji, M.; Kasper, D. L.; *Nat. Med.* **2011**, *17*, 1602-1610.
(10) Danishefsky, S. J.; Shue, Y.; Chang, M. N.; Wong, C.; *Acc. Chem. Res.* **2015**, *48*, 643-652.